Fluosilicate; Sodium Hexafluorosilicate; Кремнефтористый Натрий.
Na_2SiF_6=188.1.
CAS — 16893-85-9.
UNII — 806AV2E065.

Profile

Sodium silicofluoride is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) for the fluoridation of drinking water. It has also been considered for inclusion in oral hygiene products.

Other silicofluoride (fluorosilicate) salts permitted for use in oral hygiene products include ammonium silicofluoride, magnesium silicofluoride, and potassium silicofluoride.

Sodium silicofluoride has also been used in insecticides.

Sorbitol

E420; D-Sorbitol; Sorbitoli; Sorbitolis; Sorbitolum; Szorbit; Сорбит; Сорбитол.
D-Glucitol.
$C_6H_{14}O_6$=182.2
CAS — 50-70-4.
ATC — A06AD18; A06AG07; B05CX02; V04CC01.
ATC Vet — QA06AD18; QA06AG07; QB05CX02; QV04CC01.
UNII — 506T60A25R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *Viet.* Also in *USNF.*

US includes only Sorbitol Solution.

Ph. Eur. 8: (Sorbitol). A white or almost white crystalline powder. It exhibits polymorphism. Very soluble in water; practically insoluble in alcohol.

USNF 31: (Sorbitol). White, odourless, hygroscopic powder, granules, or crystalline masses having a sweet taste with a cold sensation. Soluble 1 in 0.45 of water; sparingly soluble in alcohol; practically insoluble in solvent ether. pH of a 10% w/w solution in water is between 3.5 and 7.0.

Incompatibility. For reference to the incompatibility of sorbitol with hydroxybenzoates, see p. 1757.3.

Uses and Administration

Sorbitol is a polyhydric sugar alcohol (polyol) with about half the sweetening power of sucrose. It occurs naturally in many fruits and vegetables and is prepared commercially by the reduction of glucose.

It has been given as a 30% solution as an alternative to glucose in parenteral nutrition (p. 2044.1) but its use is not recommended because of the risk of lactic acidosis.

Sorbitol may be given as an osmotic laxative in the management of constipation (p. 1804.3); daily doses of about 14 to 42 g orally, or 30 to 36 g rectally have been used.

Solutions containing about 3% of sorbitol are used as irrigating fluids in transurethral surgical procedures.

Sorbitol was formerly given intravenously as a 50% solution as an osmotic diuretic.

Sorbitol also acts as a bulk sweetening agent. It is used in limited quantities as a sweetener in energy-reduced diabetic food products. It is also used as an alternative to sucrose in many sugar-free oral liquid preparations and in sugar-free foods as it is less likely to cause dental caries.

Sorbitol also has humectant and stabilising properties and is used in various pharmaceutical and cosmetic products including toothpaste.

Adverse Effects and Precautions

As for Fructose, p. 2068.2.

Effects on electrolyte balance. Sorbitol is used as a vehicle in some proprietary preparations of activated charcoal intended to reduce drug absorption after poisoning; the sorbitol increases the palatability of the preparation and also produces an osmotic diarrhoea that facilitates elimination of the activated charcoal and adsorbed drug. Repeated doses of such preparations are often advocated but there have been reports[1-3] of severe sorbitol-induced hypernatraemia in adults and children. In all cases, charcoal in a 70% sorbitol suspension had been given. It has been recommended that fluid and electrolyte balance be monitored closely, and that preparations with lower concentrations of sorbitol be used if possible.[2,3] For debate about such multiple dose therapy see Poisoning, under Activated Charcoal, p. 1538.1.

1. Gazda-Smith B, Synhavsky A. Hypernatraemia following treatment of theophylline toxicity with activated charcoal and sorbitol. *Arch Intern Med* 1990; **150**: 689 and 692.
2. Allerton JP, Strom JA. Hypernatremia due to repeated doses of charcoal-sorbitol. *Am J Kidney Dis* 1991; **17**: 581–4.
3. Farley TA. Severe hypernatremic dehydration after use of an activated charcoal-sorbitol suspension. *J Pediatr* 1986; **109**: 719–22.

Effects on the gastrointestinal tract. Sorbitol is often used as a sweetener in sugar-free preparations and the risk of sorbitol-induced diarrhoea associated with such products has been highlighted.[1-4] Chronic sorbitol-induced diarrhoea with associated pneumatosis intestinalis has been reported in a child given 21.7 g sorbitol daily in liquid medications.[5] Colonic and upper gastrointestinal necrosis, including some fatalities, have been reported after use of sodium polystyrene sulfonate in sorbitol, and may have been associated with the sorbitol component, see p. 1575.3.

It has also been suggested that sorbitol contributed to the morbidity in a patient who developed septicaemia as a complication of intestinal pseudo-obstruction, after the use of charcoal with sorbitol to treat self-poisoning with theophylline.[6] It was suggested that gaseous distension after bacterial metabolism of sorbitol had rendered the bowel wall ischaemic, facilitating passage of bacteria or of endotoxin into the systemic circulation.

1. Brown AM, Masson E. Hidden' sorbitol in proprietary medicines - a cause for concern? *Pharm J* 1990; **245**: 211.
2. Edes TE, *et al.* Diarrhea in tube-fed patients: feeding formula not necessarily the cause. *Am J Med* 1990; **88**: 91–3.
3. Johnston KR, *et al.* Gastrointestinal effects of sorbitol as an additive in liquid medications. *Am J Med* 1994; **97**: 185–91.
4. Bauditz J, *et al.* Severe weight loss caused by chewing gum. *BMJ* 2008; **336**: 96–7.
5. Duncan B, *et al.* Medication-induced pneumatosis intestinalis. *Pediatrics* 1997; **99**: 633–6.
6. Longdon P, Henderson A. Intestinal pseudo-obstruction following the use of enteral charcoal and sorbitol and mechanical ventilation with papaveretum sedation for theophylline poisoning. *Drug Safety* 1992; **7**: 74–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sorbitol 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 07/10/11)

Pharmacokinetics

Sorbitol is poorly absorbed from the gastrointestinal tract after oral or rectal use. It is metabolised mainly in the liver, to fructose (see p. 2068.3), a reaction catalysed by the enzyme sorbitol dehydrogenase. Some sorbitol may be converted directly to glucose by the enzyme aldose reductase.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Sorbilax; *Braz.*: Minilax; *Rus.*: Sorbit (Сорбит); *Swed.*: Resulax.

Multi-ingredient Preparations. *Arg.*: Humectante Bucal; Micronema; *Austral.*: Aquae; Carbosorb XS; Fleet Micro-Enema†; Microlax; *Austria*: Glandosane; Microklist; Yal; *Belg.*: Microlax; Spagulax Sorbitol†; *Braz.*: Anekron; Colachofra; Hepalin; Hepatox; *Canad.*: Charac Tol; Charcodote; Microlax; Moi-Stir; *Chile*: Secand; Solucion Irrigacion Vesical†; Tabletas Phillips; Ureadin Rx PS; *Cz.*: Yal; *Denm.*: Klyx; *Fin.*: Klyx; Microlax; *Fr.*: Actigess†; Apilaxe; Artisial; Cicatridine; Hepagrume; Hepargitol; Microlax; Nivabetol†; Parapsyllium; Schoum; Spagulax au Sorbitol†; SST†; *Ger.*: Flacar; Freka-Drainjet Purisole†; Glandosane; Microklist; Saliva natura; Xerotin; Yal; *Gr.*: Collyre Vitaphakol; Suprin; *Hong Kong*: Glandosane; Microlax†; Osmofundin†; Salivart†; *Hung.*: Balansol; Rehydrosol†; *India*: Al-Live; Alkasol-P; Aminocore 5-S Plus; Aminofusion; Anorexin Plus; Aqvet; Bioferum Forte; Bioffin; Brofentol; Celemin; Celemix Combi; Cyaptin-SF; Cyaptin; Cyp-L; Cypine-TS; Cypolin; Cypon-L; Cyprea-T/ Cyprobit; Decyp-P; Perricos; Ferritop Iron Tonic; Ferrofit; Porliv; Fortil; Gastrozyme; Gelusil Plus; Growise; Haematinga; Hb-Rich; Hepachol; Hepoline; Hermin; Livocip; Mecolin; Siloxogene; Sorbiline; Sorliv; *Indon.*: Aminofusin L; Aminovel; Amnorel; Celemin; Ferobion; Intrafusin SX-E; Laxarec; Microlax; Nutrisol-S; Pan Amin G; Pronita; Tutofusin LC; Tutofusin OpS; Valamin; *Israel*: Biolax Protect; Biolax†; Charcodote; Spray Mint; *Ital.*: Citroepatina†; Macrolax; Novilax; Sorbidis; *Jpn*: Lactec G; *Mex.*: Clyss-Go; *Neth.*: Klyx; Microlax; *Norw.*: Klyx; Microlax; *NZ*: Carbosorb XS; Microlax; *Pol.*: Purisole SM†; Rektiolax; *Port.*: Clyss-Go; Glandosane†; Purisole; *Rus.*: Aminosol (Аминосол); Hepasol A (Гепасол А); Highmix (Хайомикс); Microlax (Микролакс); Reosorbilact (Реосорбилакт); Sorbilact (Сорбилакт); *S.Afr.*: Agofell†; *Singapore*: Charcodote; Microlax; Minica S; Osmofundin; *Spain*: Sugarbil†; *Swed.*: Klyx; Microlax; Omnilax; *Switz.*: Agarol Soft†; Glandosane; Microklist; Microlax; Pursana; Yal; *Thal.*: Glandosane; *Turk.*: Charflo Sorbitol†; Kanslak; Libalaks; Sabalaks; Yal; *UK*: Glandosane; Luborant†; Relaxit; Saliva Natura; SST; Xerotin; *Ukr.*: Hepasol A (Гепасол А); Lactoprotein-C (Лактопротеин-С); Reosorbilact (Реосорбилакт); Rheosorbilact (Реосорбилакт); Sorbilact (Сорбилакт); Turusol (Турусол); *USA*: Actidose with Sorbitol; Moi-Stir; Numoisyn; Plax; Salivart.

Pharmacopoeial Preparations

Ph. Eur.: Sorbitol, Liquid (Crystallising); Sorbitol, Liquid (Non-crystallising); Sorbitol, Liquid, Partially Dehydrated;
USNF 31: Noncrystallizing Sorbitol Solution;
USP 36: Sorbitol Solution.

Soya Bean

Habas de Soja; Soja Bean; Soyabean; Soybean; Соевый Боб.
ATC Herb — HA10BX5002 (Glycine max: seed).
UNII — L7HT8F1ZOD.

Description. Soya bean is the seed of the soya plant *Glycine max* (*G. hispida*; *G. soja* (L.) Merr.). It is a source of soya oil and soya protein. *G.soja* Siebold & Zucc. is wild soybean.

Soya Oil

Aceite de soja; Soiae Oleum; Soijaöly; Sojų aliejus; Soja Bean Oil; Soja, huile de; Sojae oleum; Sojaolja; Sójový olej; Soya Yağı; Soya-bean Oil; Soyabean Oil; Soybean Oil; Szójababolaj; Соевое Масло.
CAS — 8001-22-7.
ATC Herb — HD02WB5002 (Glycine max: oil); HB05BA5003 (Glycine max: oil).
UNII — 241ATL177A (soya oil); A2M91M918C (hydrogenated soya oil).

Pharmacopoeias. In *Chin.*, *Jpn*, and *US.*

Eur. (see p. vii) includes both hydrogenated and refined oils. *Ger.* also includes a partially hydrogenated oil. *USNF* includes the hydrogenated oil.

Ph. Eur. 8: (Soya-bean Oil, Refined; Soiae Oleum Raffinatum). It is the fatty oil obtained from seeds of *G. max* (*G. hispida*) by extraction and subsequent refining. It may contain a suitable antoxidant and is a clear, pale yellow liquid. Practically insoluble in alcohol; miscible with petroleum spirit. Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light.

The BP 2014 directs that when Soya Oil, Soyabean Oil, or Soya-bean Oil is demanded, Refined Soya Oil shall be supplied.

Ph. Eur. 8: (Soya-bean Oil, Hydrogenated; Soiae Oleum Hydrogenatum). It is obtained by refining, bleaching, hydrogenation, and deodorisation of soya oil. It consists mainly of triglycerides of palmitic and stearic acids and is a white or almost white mass or powder which melts to a clear, pale yellow liquid when heated. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane, in petroleum spirit after heating, and in toluene. Protect from light.

USP 36: (Soybean Oil). The refined fixed oil obtained from the seeds of the soya plant *Glycine max* (Fabaceae). It may contain suitable antoxidants. A clear, pale yellow, oily liquid having a characteristic odour. Insoluble in water; miscible with chloroform and with ether. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

USNF 31: (Hydrogenated Soybean Oil). The product obtained by refining, bleaching, hydrogenation, and deodorisation of oil obtained from seeds of the soya plant, *Glycine max* (Fabaceae). It consists mainly of triglycerides of palmitic and stearic acids. A white mass or powder that melts to a clear, pale yellow liquid when heated. M.p. between 66 degrees and 72 degrees. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane, in petroleum spirit after heating, and in toluene. Store in airtight containers. Protect from light.

Incompatibility. For mention of the stability and compatibility of solutions and emulsions for parenteral nutrition see under Enteral and Parenteral Nutrition, p. 2044.2.

Uses and Administration

Emulsions of fractionated soya oil containing 10, 20, or 30% are given by slow intravenous infusion as part of total parenteral nutrition regimens (p. 2044.1), usually with amino acid and carbohydrate solutions. The solutions and emulsions may be given at separate sites, at the same site through a Y-connector, or combined in one admixture. Fat emulsions provide a high energy intake in a relatively small volume. They may also be used to prevent or correct essential fatty acid deficiency. When used as a calorie source the dose of the emulsion is determined by the energy requirements and clinical status of the patient; the amount of total carbohydrate, generally, should not comprise more than 60% of patients' total calorie intake. For the prevention and correction of fatty acid deficiency about 5 to 10% of total calorific intake should be as an intravenous fat emulsion.

The composition and dosage recommendations of commercial preparations do differ slightly but they should be started slowly. Suggested initial rates for the 10% and 20% products are 1 mL/minute and 0.5 mL/minute respectively for 15 to 30 minutes. The rate may then be increased and up to about 500 mL (or 10 mL/kg) of 10% or

250 mL (or 5 mL/kg) of 20% emulsion may be given on the first day. The total daily dosage may then be increased gradually on subsequent days; suggested daily dose ranges are 500 to 1500 mL of a 10% or 500 to 1000 mL of a 20% emulsion and suggested rates of infusion are 500 mL of a 10% emulsion over a period of not less than 3 hours, and 500 mL of a 20% emulsion over not less than 5 hours. Where a 30% emulsion is used, a dose of 333 mL or about 4.75 mL/kg has been recommended, given over 5 hours or more; the first dose should not exceed 3 mL/kg.

Soya oil also has emollient properties and is used as a bath additive in the treatment of dry skin conditions.

Preparations made from whole soya beans, containing soya oil and soya protein, are used as the basis of lactose-free vegetable milks for infants and patients with lactose or similar disaccharide intolerance or with an allergy to cow's milk protein (see also Food Intolerance, below).

Administration. It has been suggested[1] that it is the concentration of phospholipid solubilisers, and particularly the excess present as free phospholipid liposomes, that determines the effect of lipid emulsions on plasma-lipid concentrations. In 20 premature infants requiring parenteral nutrition, infusion of up to 4 g/kg of fat daily as a 20% emulsion had less effect on plasma lipid concentrations than 2 g/kg daily as a 10% emulsion; the difference was thought to be due to the fact that the 20% emulsion was relatively liposome-poor, with a ratio of phospholipids to triglycerides of 0.06, whereas the liposome-rich 10% emulsion had a ratio of 0.12. The authors suggested that the 10% emulsion should not be used in preterm infants. Others noted similar results;[2] a 10% lipid emulsion with a reduced phospholipid content has, however, been reported to be relatively well tolerated in premature infants.[3]

For mention of the risk of kernicterus if lipid infusions are given to hyperbilirubinaemic neonates, see under Precautions, p. 2094.2.

1. Haumont D, *et al.* Effect of liposomal content of lipid emulsions on plasma lipid concentrations in low birth weight infants receiving parenteral nutrition. *J Pediatr* 1992; 121: 759–63.
2. Cairns PA, *et al.* Tolerance of mixed lipid emulsion in neonates: effect of concentration. *Arch Dis Child Fetal Neonatal Ed* 1996; 75: F113–F116.
3. Gohlke BC, *et al.* Serum lipids during parenteral nutrition with a 10% lipid emulsion with reduced phospholipid emulsifier content in premature infants. *J Pediatr Endocrinol Metab* 1997; 10: 505–9.

Cardiotoxicity. Intravenous infusion of lipid emulsions has been proposed for the treatment of refractory cardiotoxicity caused by lipophilic local anaesthetics such as bupivacaine,[1,2] possibly acting in part as a 'lipid sink' into which the drugs partition, removing them from the tissues. A patient in whom prolonged cardiac arrest, unresponsive to conventional management, developed after interscalene block with bupivacaine and mepivacaine, was given a 100 mL bolus of a 20% lipid emulsion via the peripheral intravenous catheter, which resulted in almost immediate resumption of sinus rhythm;[3] the patient was subsequently given an infusion of the emulsion at a rate of 0.5 mL/kg per minute over 2 hours, and remained in sinus rhythm. There was no evidence of complications related to the use of lipid emulsion over the following 2 weeks. A subsequent case of refractory asystole subsequent to brachial plexus block with ropivacaine[4] also responded to a 100 mL bolus of 20% lipid emulsion, followed by a continuous infusion at a rate of 0.2 mL/kg per minute (total dose 4 mL/kg).

Although there have been concerns about the longer term safety of a large lipid burden, and a lack of consensus about the appropriateness of the treatment given the scanty evidence base, a protocol has been suggested[1] on the basis of case reports and *animal* studies. Treatment, which is reserved for patients with local anaesthetic cardiotoxicity resistant to standard resuscitation, is to continue advanced cardiac life support measures (see Cardiac Arrest, p. 1268.3) plus:

- intravenous bolus of 20% lipid emulsion (*Intralipid*) at a dose of 1.5 mL/kg, *followed by*
- continuous infusion of the emulsion at a rate of 0.25 mL/kg per minute for 30 minutes; if blood pressure declines, rate may be increased to 0.5 mL/kg per minute. The infusion may be continued for up to an hour if appropriate, and may need to be restarted if blood pressure declines when it is stopped

If there is no response to the bolus it may be repeated once or twice; additional boluses are not likely to be required once sinus rhythm returns, even though ventricular ectopy or other arrhythmias may persist.

The technique may be appropriate for other lipophilic drugs that cause refractory cardiotoxicity—for mention of its use to treat verapamil toxicity after overdosage with a modified-release formulation, see p. 1524.2.

1. Weinberg G. Lipid rescue resuscitation from local anaesthetic cardiac toxicity. *Toxicol Rev* 2006; 25: 139–45.
2. Leskiw U, Weinberg GL. Lipid resuscitation for local anesthetic toxicity: is it really lifesaving? *Curr Opin Anaesthesiol* 2009; 22: 667–71.
3. Rosenblatt MA, *et al.* Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. *Anesthesiology* 2006; 105: 217–18.
4. Litz RJ, *et al.* Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. *Anaesthesia* 2006; 61: 800–1.

Food intolerance. The American Academy of Pediatrics has recommended[1] that soya-based infant feeds are appropriate for use in galactosaemia and hereditary lactase deficiency, and may be an alternative for families who wish to avoid using infant feeds containing animal products. Extensively hydrolysed protein feeds should be considered for documented allergy to cow's milk protein, as 10 to 14% of these infants will also have a soy protein allergy. Infants with cow's milk-protein-induced enteropathy or enterocolitis are also very likely to be sensitive to soy protein, and should again receive a feed derived from hydrolysed protein, or synthetic amino acids. After rehydration for acute gastroenteritis, most previously healthy infants can continue to have human milk or cow milk feeds, but soy-based infant feeds may be indicated when secondary lactose intolerance occurs. The Academy concluded that soya-based infant feeds are not recommended for preterm infants and have no proven role in the prevention of atopic disease or in the management of infantile colic. In infants and children at high risk for developing food allergies or intolerance, a systematic review[2] found that there was no evidence that feeding with a soy formula compared with a cow's milk formula reduced the incidence of food allergies or intolerance.

The FDA has warned against the use of soya-based drinks intended for adults as the sole source for nutrition for infants.[3] It was stated that soya drinks can lead to severe protein and calorie malnutrition, multiple vitamin and mineral deficiency, and death in infants who receive no other source of nourishment, and should not be confused with soya-based infant formulas, which are specially formulated to meet the nutritional needs of infants.

For reference to the use of soya-based foods themselves causing allergic reactions, see under Hypersensitivity, p. 2094.1.

1. Bhatia J, Greer F. American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics* 2008; 121: 1062–8. Also available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/1062 (accessed 27/01/10)
2. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 08/11/05).
3. Nightingale S. Warnings issued about practices, products: soy drink warning. *JAMA* 1985; 254: 1428.

Hyperlipidaemias. Soya protein has been tried in the treatment of hyperlipidaemia (p. 1248.1). Soya isoflavones such as genistein (p. 2620.3) and daidzein (p. 2620.3) can mimic oestrogen and should therefore have a beneficial effect on blood lipids.[1,2] Other constituents of soya protein, including fytic acid and saponins, may also contribute and thus intact soya protein may provide the maximum cholesterol-lowering effect.[2,3] A meta-analysis of controlled trials found that the substitution of soya protein for animal protein in the diet resulted in significant decreases in serum total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglyceride concentrations.[4] A subsequent systematic review of studies reached similar conclusions,[1] and the FDA considered that a low-fat diet including 25 g daily of soya protein might reduce the risk of ischaemic heart disease.[2] A later analysis by the American Heart Association[5] considered that cardiovascular benefit was very modest and appeared only when large amounts of animal protein were substituted with soya protein. The effect appeared to be more to do with a broader modification of diet than any effect of soya isoflavones. Soya protein does not appear to have a cholesterol-lowering effect in subjects with normal cholesterol concentrations,[2] although a small study found it to be beneficial in type 2 diabetes patients with near-normal lipid concentrations.[6]

1. Costa RL, Summa MA. Soy protein in the management of hyperlipidemia. *Ann Pharmacother* 2000; 34: 931–5.
2. Erdman JW. Soy protein and cardiovascular disease: a statement for healthcare professionals from the Nutrition Committee of the AHA. *Circulation* 2000; 102: 2555–9.
3. Demonty I, *et al.* Role of isoflavones in the hypocholesterolemic effect of soy. *Nutr Rev* 2003; 61: 189–203.
4. Anderson JW, *et al.* Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995; 333: 276–82.
5. Sacks FM, *et al.* Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation* 2006; 113: 1034–44. Also available at: http://circ.ahajournals.org/cgi/reprint/113/7/1034.pdf (accessed 20/03/09)
6. Hermansen K, *et al.* Beneficial effects of a soy-based dietary supplement on lipid levels and cardiovascular risk markers in type 2 diabetic subjects. *Diabetes Care* 2001; 24: 228–33.

Menopausal disorders. Soya contains phytoestrogens in the form of isoflavones, in particular daidzein (p. 2620.3) and genistein (p. 2620.3), which have been investigated for their oestrogen-modulating effects in the treatment of symptoms associated with menopausal disorders—see under Soya Isoflavones, p. 2620.3.

Osteoarthritis. For mention of the possible benefits of a mixture of avocado and soya oils (avocado-soybean unsaponifiables) for symptomatic relief in patients with osteoarthritis, see p. 2451.2.

Adverse Effects

Hypersensitivity reactions including fever and chills have been reported after the infusion of soya oil emulsion although they are considered to be fairly rare. Other rare immediate reactions include dyspnoea, cyanosis, hyperlipidaemia, hypercoagulability, nausea, vomiting, headache, and chest and back pain. Delayed reactions include hepatomegaly, splenomegaly, jaundice due to cholestasis, thrombocytopenia, leucopenia, and transient increases in liver function tests.

Prolonged or too rapid infusion of soya oil emulsion or its use in patients with impaired fat metabolism has been associated with the 'overload syndrome'. This is manifested by anaemia, leucocytopenia, thrombocytopenia, and impaired coagulation, hepatosplenomegaly, hyperlipidaemia, fever, focal seizures, shock, and coma. Metabolic acidosis has been associated with severe overdosage especially if carbohydrates are not also given. Pigmentation of tissues in the reticuloendothelial system after prolonged therapy with lipid emulsion infusions has also been reported.

Soya protein-based infant feeds can be antigenic and cause gastrointestinal adverse effects in sensitive individuals.

Bacteraemia. A strong association has been found between giving lipids through peripheral venous catheters made of Teflon and development of coagulase-negative staphylococcal bacteraemia in neonates.[1] It was suggested that investigation of catheters made of other materials, or other delivery systems, might reduce the opportunity for coagulase-negative staphylococci to adhere and come into contact with nutrient-rich growth media in the form of lipid emulsions. Others also took the view that this work should not lead to the abandonment of parenteral lipids in premature infants.[2]

1. Freeman J, *et al.* Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N Engl J Med* 1990; 323: 301–8.
2. Klein JO. From harmless commensal to invasive pathogen: coagulase-negative staphylococci. *N Engl J Med* 1990; 323: 339–40.

Effects on the cardiovascular system. Sinus bradycardia has been reported in a patient receiving total parenteral nutrition that included soya oil-based emulsion via a central line.[1] The authors suggested that it might be wise to give fat emulsion only through a peripheral vein. However, sinus bradycardia has been reported after a safflower oil-based emulsion given via a peripheral vein as part of a TPN regimen.[2]

1. Sternberg A, *et al.* Intralipid-induced transient sinus bradycardia. *N Engl J Med* 1981; 304: 422–3.
2. Traub SL, *et al.* Sinus bradycardia associated with peripheral lipids and total parenteral nutrition. *J Parenter Enteral Nutr* 1985; 9: 358–60.

Effects on the endocrine system. Soya bean is a rich source of phytoestrogens including isoflavones, and it has been found that infants fed soya-based formula have high serum concentrations of these substances,[1] which has brought the safety of soya-based formulas into question. *Animal* and *in vitro* data suggest that isoflavones such as genistein have pharmacological effects on growth and development.[2] However, genistein and daidzein are less potent than endogenous oestrogens and have less binding affinity to oestrogen receptors.[3] It is not known to what extent infants are able to metabolise and deconjugate soya isoflavones.[4] A small retrospective study[5] found no oestrogenic effects in children fed soya protein formula for at least 6 months. A larger retrospective cohort study[6] in adults observed no statistically significant differences between those who had been fed soya formula and those fed cow's milk formula as infants.

As yet, there is insufficient evidence of harm from soya-based formulas,[7] although further studies are deemed necessary to assess long-term effects.[2,4] The American Academy of Pediatrics[8] considers soya protein-based formulas to be safe and effective in healthy term infants, while providing no advantage over cow's milk protein-based formulas. However, soya-based formulas are not recommended for use in preterm infants because of concerns about poorer bone development compared with infants given formulas based on cow's milk protein.

Before their supplementation with iodine, there had been reports of hypothyroidism associated with soya formula feeds. Abnormal thyroid function tests have since been reported in infants fed with soya formulas, and a retrospective analysis of infants with congenital hypothyroidism found those fed with soya took longer for their thyroid stimulating hormone levels to normalise.[9]

1. Setchell KDR, *et al.* Exposure of infants to phyto-oestrogens from soy-based infant formula. *Lancet* 1997; 350: 23–7.

2. Chen A, Rogan WJ. Isoflavones in soy infant formula: a review of evidence for endocrine and other activity in infants. *Annu Rev Nutr* 2004; 24: 33–54.
3. Miniello VL, *et al.* Soy-based formulas and phyto-oestrogens: a safety profile. *Acta Paediatr Suppl* 2003; 91: 93–100.
4. Mendez MA, *et al.* Soy-based formulae and infant growth and development: a review. *J Nutr* 2002; 132: 2127–30.
5. Giampietro PG, *et al.* Soy protein formulas in children: no hormonal effects in long-term feeding. *J Pediatr Endocrinol Metab* 2004; 17: 191–6.
6. Strom BL, *et al.* Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA* 2001; 286: 807–14.
7. Tuohy PG. Soy infant formula and phytoestrogens. *J Paediatr Child Health* 2003; 39: 401–5.
8. Bhatia J, Greer F. American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics* 2008; 121: 1062–8. Also available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/1062 (accessed 27/01/10)
9. Conrad SC, *et al.* Soy formula complicates management of congenital hypothyroidism. *Arch Dis Child* 2004; 89: 37–40.

Effects on the nervous system. CNS disorders in 2 patients given infusions of fractionated soya emulsion included convulsions and coma; cortical blindness developed in one young woman.[1] A similar case was attributed to fat embolism,[2] but, occurring after what the manufacturers pointed out was a faster than recommended infusion,[3] may perhaps have represented a fat-overload syndrome. Neurological complications can be the presenting and principal signs of fat overload: focal and generalised seizures, weakness, and encephalopathy have been reported.[4]

Migraine with visual aura has also been reported in a 57-year old man taking soya beans, soya milk, and a soya protein supplement.[5]

1. Jellinek EH. Dangers of intravenous fat infusions. *Lancet* 1976; ii: 967.
2. Estebe JP, Malledant Y. Fat embolism after lipid emulsion infusion. *Lancet* 1991; 337: 673.
3. McCracken M. Fat embolism after lipid emulsion infusion. *Lancet* 1991; 337: 983.
4. Schulz PE, *et al.* Neurological complications from fat emulsion therapy. *Ann Neurol* 1994; 35: 628–30.
5. Engel PA. New onset migraine associated with use of soy isoflavone supplements. *Neurology* 2002; 59: 1289–90.

Hypersensitivity. Urticaria has been reported in 2 patients after the intravenous use of soya oil emulsions.[1,2] In one case the patient had previously received the emulsion for 19 days without ill-effect.[1]

Anaphylactic reactions have been documented after the ingestion of several foods or foodstuffs containing, or prepared from, soya beans, although the exact allergen remains unknown. In one patient who suffered anaphylactic attacks after eating such products a specific IgE-antibody response to the allergen Kunitz soybean trypsin inhibitor was demonstrated.[3] This was not, however, the only allergen present in soya beans as other patients who had a negative response to this allergen had positive responses in whole soya bean tests. A type I reaction to soya bean protein has been described in patients given parenteral lipid emulsions containing soya bean lecithin as the emulsifier.[4] A patient who ingested a soya protein drink experienced exercise-induced anaphylaxis; skin prick tests were positive to soya, but specific IgE antibodies to soya were undetectable.[5]

IgE antibodies to soya bean antigens have also been found in workers who suffered from asthma after handling soya beans[6,7] leading to the suggestion that an allergic mechanism had been responsible; the asthma was believed to have been due to the dust released during the handling of the beans.

1. Kamath KR, *et al.* Acute hypersensitivity reaction to Intralipid. *N Engl J Med* 1981; 304: 360.
2. Hiyama DT, *et al.* Hypersensitivity following lipid emulsion infusion in an adult patient. *J Parenter Enteral Nutr* 1989; 13: 318–20.
3. Moroz LA, Yang WH. Kunitz soybean trypsin inhibitor: a specific allergen in food anaphylaxis. *N Engl J Med* 1980; 302: 1126–8.
4. Weidmann B, *et al.* Hypersensitivity reactions to parenteral lipid solutions. *Support Care Cancer* 1997; 5: 504–5.
5. Taramarcaz P, *et al.* Soy anaphylaxis. *Allergy* 2001; 56: 792.
6. Sunyer J, *et al.* Case-control study of serum immunoglobulin-E antibodies reactive with soybean in epidemic asthma. *Lancet* 1989; i: 179–82.
7. Hernando L, *et al.* Asthma epidemics and soybean in Cartagena (Spain). *Lancet* 1989; i: 502.

Pulmonary fat emboli. Pulmonary fat emboli or microemboli, sometimes fatal, have occurred in several infants who received infusions of fat emulsions based on soya oil.[1-3]

In one case[3] the patient's serum, which contained a high concentration of C-reactive protein, agglutinated the fat emulsion and this finding was considered to support the hypothesis that microemboli are formed by agglutination of fat emulsion in the blood by C-reactive protein. The authors of this report did not consider the precise pathogenesis to be clear, nor did they know whether the condition was preventable, but did suggest that it might be prudent either to ensure that the C-reactive protein concentration was normal (less than 10 mg/litre) or to perform a creaming test to determine which babies may embolise the infused fat emulsion. However, another study,[4] while not excluding a role of C-reactive protein in agglutination, failed to find any correlation between raised concentrations of this protein and the rate of agglutination. A review[5] classified fat embolism into those derived from direct entry of depot fat into the blood (e.g. after trauma), and those derived from agglutination of endogenous or exogenous fat. High concentrations of C-reactive protein were considered to be responsible for the agglutination of the liposomes of fat emulsions; chylomicrons and very low-density lipoproteins in the blood may also agglutinate, contributing to fat embolism.

1. Barson AJ, *et al.* Fat embolism in infancy after intravenous fat infusions. *Arch Dis Child* 1978; 53: 218–23.
2. Levene ML, *et al.* Pulmonary fat accumulation after Intralipid infusion in the preterm infant. *Lancet* 1980; ii: 815–8.
3. Hulman G, Levene M. Intralipid microemboli. *Arch Dis Child* 1986; 61: 702–3.
4. Zagara G, *et al.* C-reactive protein and serum agglutination in vivo of intravenous fat emulsions. *Lancet* 1989; i: 733.
5. Hulman G. The pathogenesis of fat embolism. *J Pathol* 1995; 176: 3–9.

Precautions

Intravenous soya oil emulsion should not be given to patients with severe liver disease, acute shock, or severe or pathological hyperlipidaemia, or when the ability to metabolise fat may otherwise be impaired. Caution has also been advised in patients with pulmonary disease, renal insufficiency, uncompensated diabetes mellitus and other metabolic disorders, sepsis, anaemia, and some disorders of blood coagulation. If given to such patients, the elimination of fat should be monitored daily.

Intravenous soya oil emulsion may interfere with some laboratory tests if blood is taken before fat has adequately cleared; this may take 4 to 6 hours.

Egg-yolk phospholipids may be used as emulsifiers in some preparations, which should not be given to patients with severe egg allergy.

Fat emulsions may extract phthalate plasticisers from bags and giving sets and non-phthalate containing equipment should be used wherever possible.

Soya-based infant feeds should be avoided in infants with documented cow's milk protein-induced enteropathy or enterocolitis, as these infants are often also sensitive to soya protein.

Neonatal hyperbilirubinaemia. In neonates with hyperbilirubinaemia, intravenous lipid emulsions should be used with caution because of the risk of displacing bilirubin from albumin and the resulting risk of producing kernicterus. The risk appears to be higher in preterm infants,[1] at higher doses,[1] and with intermittent rather than continuous dosing.[2]

1. Spear ML, *et al.* The effect of 15-hour fat infusions of varying dosage on bilirubin binding to albumin. *J Parenter Enteral Nutr* 1985; 9: 144–7.
2. Brans YW, *et al.* Influence of intravenous fat emulsion on serum bilirubin in very low birthweight neonates. *Arch Dis Child* 1987; 62: 156–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ivelip; Lipofundin N; Lipovenos; Piascledine; Sojar Pro; Soyacal†; ***Austral.***: Intralipid; Ivelip; ***Austria***: Balneum; Intralipid; Olbad Cordes†; ***Belg.***: Gynosoya; ***Braz.***: Fisiogen; Soyfit; ***Canad.***: Intralipid; ***Chile***: Lipofundin; Lipovenos; ***China***: Intralipid (英脱利匹特); Intralipos (力基); Ivelip (意维利匹); ***Cz.***: Balneum Hermal; Intralipid; Lipovenoes†; Soyacal†; ***Denm.***: Intralipid; ***Fin.***: Intralipid; ***Fr.***: Endolipide†; Gynalpha; Intralipide; Ivelip; Phyto Soya; SANO-Gastril; ***Ger.***: Balneoconzen N; Balneovit; Balneum; Buer Lecithin Cholesterin Balance†; Deltalipid†; Lipidavit SL; Lipofundin N; Lipopharm; Lipostabil; Lipovenos; Olbad Cordes†; salvilipid†; Soyacal†; ***Gr.***: Intralipid; Lipovenoes; ***Hong Kong***: Intralipid; Lipofundin N†; ***Hung.***: Balneum; Intralipid; Structolipid†; ***India***: Celepid; Intralipid; ***Indon.***: Celepid; Glisopos; Intralipid; Intralipos; Ivelip; Lipovenoes; ***Irl.***: Balneum†; Intralipid; ***Israel***: Balneum; Intralipid; Ivelip; ***Ital.***: Balneum Hermal; Elolipid; Intralipid; Lipofundin S; Lipovenos; ***Jpn***: Intrafat; ***Malaysia***: Intralipid†; ***Mex.***: Lipofundin N; Lipovenoes; ***Mon.***: Evestrel†; ***Neth.***: Intralipid; Lipovenos†; ***Norw.***: Intralipid; ***NZ***: Intralipid; Ivelip; ***Philipp.***: Celepid; Soyacal; ***Pol.***: Balneum Hermal†; Intralipid; Ivelip†; Lipofundin N; Soya Meno†; Soyfem; ***Port.***: Banholeum; Emulsao de Lipidos; Endolipide†; Intralipid; Lipovenoes; Soyacal; ***Rus.***: Intralipid (Интралипид); Resalut Pro (Резалют Про); ***S.Afr.***: Intralipid; ***Singapore***: Intralipid; Intralipos; Ivelip; Lipofundin N; ***Spain***: Aquiflav†; Bluna†; Fitoladius; Flavodrei; Intralipid; Isodonna†; Malena; Menodim†; Normosoy; Phyto Soya; Pleginer; Primsoja†; Ratiofemin†; Soyacal; ***Swed.***: Intralipid; ***Switz.***: Balmed Hermal Plus; Balmed Hermal; Intralipid†; Lipovenos†; ***Thai.***: Celepid†; Intralipid; Ivelip†; Lipofundin N†; Lipofundin S†; ***Turk.***: Intralipid; Ivelip; Lipovenos; ***UK***: Balneum; Intralipid; Ivelip; Lipofundin; Zeroneum; ***Ukr.***: Enerliv (Энерлив); Intralipid (Интралипид); Liventiale (Ливенциале)†; Onagris (Онагрис); ***USA***: Intralipid; Liposyn III; ***Venez.***: Ivelip.

Multi-ingredient Preparations. ***Arg.***: Clinoleic; Derrumal; Kabiven; Lecitina E; Lipofundin MCT/LCT-E†; Lipofundin MCT/LCT; Liposomas; Lipovenos MCT/LCT; Lipovenos PLR; Puraplus; Sigmafem; Sojar Plus-Calcio; Ukase Lulitis; ***Austral.***: Clinoleic; EFA Compound; Extralife Meno-Care†; GR² Control Appetite Reducer; Hypol; Kabiven; Mens Super Soy/Clover†; PhytoLife; PM H-Regulator; SMOFlipid; Soy Power Plus†; Tre-en-en; ***Austria***: Balneum Plus; Clinoleic; Kabiven†; Lipidem; Lipofundin mit MCT; Nutriflex Lipid; OliClinomel; PE-Mix†; PeriOlimel; SMOFlipid; Structolipid†; Vitromix; ZentroOlimel; ***Belg.***: Clinoleic; Lipoplus; Medialipide; Nutriflex Lipid; OliClinomel; Olimel; PeriOlimel; ***Braz.***: Borag; Emulsao Scott; Piascledine; Votag O6; ***Canad.***: Clinoleic; Liposyn; Olimel; PeriOlimel; ***Chile***: Cellenergy; Hyaluron; Kabiven; Lipofundin MCT/LCT; Lipovenos MCT/LCT; OliClinomel; Piascledine; ***China***: Lipofundin MCT/LCT (力保肪宁); Lipovenoes (力能); ***Cz.***: Balneum Hermal Plus; Clinoleic; Kabiven; Lipofundin MCT/LCT†; Lipoplus; Nutriflex Lipid; NuTRIflex Omega; OliClinomel; Olimel; PeriOlimel; Piascledine; SMOFKabiven; SMOFlipid; ***Denm.***: Clinoleic; Kabiven; Lipidem; Numeta GE; Nutriflex Lipid; OliClinomel†; Olimel; SMOFKabiven; SMOFlipid; Vasolipid; ***Fin.***: Clinoleic; Kabiven; Lipoplus; Numeta GE; Nutriflex Lipid; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Structolipid; Vasolipid; ***Fr.***: Alpharegul Homme; Biopause; Clinoleic; Elteans; Fadiamone; Gynalpha Plus†; Kabiven; Kotor Meno; Lipidem; Medialipide; Mednutriflex Lipide G; Nutriflex Lipide†; OliClinomel; Olimel; Oxelio; Perikabiven; PeriOlimel; Pharyndol; Piascledine; Reanutriflex Lipide; Reanutriflex Omega; SMOFKabiven; SMOFlipid; StructoKabiven; Structolipide†; Synaptiv; Vitrimix†; ***Ger.***: Balneum Plus; Clinoleic; Kabiven; Lipidem; Lipofundin MCT; Lipovenos MCT; Numeta GE; Nutriflex Lipid; NuTRIflex Omega; Oleobal; OliClinomel†; Olimel; SMOFKabiven; SMOFlipid; ***Gr.***: Clinoleic; Clinomel; Compleven; Kabiven; Lipofundin MCT/LCT; Lipoplus; Multimel; Nutriflex Lipid; OliClinomel; SMOFKabiven; SMOFlipid; Trive-1000; ***Hong Kong***: Kabiven; Lipofundin MCT/LCT; Nutriflex Lipid; SMOFlipid; Vitrimix KV†; ***Hung.***: Allice; Balneum Hermal Plus; Kabiven; Lipofundin MCT†; OliClinomel; SMOFlipid; ***India***: Celepid MCT-LCT; Familykair; Gynerol; Hemofit; Kabiven; Lipofundin MCT/LCT; Nutrilex Lipid Peri; Osteoshield; ***Indon.***: Hepabion†; Kabiven; Lanaven; Lipofundin MCT/LCT†; Lipomed MCT/LCT; Maxitrin†; Vitrimix†; ***Irl.***: Balneum Plus†; Clinoleic†; KabiMix†; Kabiven; Lipidem; Lipofundin MCT/LCT†; Numeta GE; Nutriflex Lipid; OliClinomel; SMOFKabiven; SMOFlipid; Structolipid†; Triomel; Vitrimix KV†; ***Israel***: Balneum Plus; Clinoleic; Kabiven; Lipofundin MCT/LCT; OliClinomel; SMOFKabiven; SMOFlipid; ***Ital.***: Acumel; Anti-Ves; Assist; Bioestril Ginseng; Bioestril Valeriana; Biomineral 5-Alfa; Clinoleic; Demalit; Eavit Plus; Fitogen; Ginil; Kabiven; Lipidem; Lipimix; Lipofundin MCT; Liposyn; Nutriperi Lipid; Nutriplus Lipid; Nutrispecial Lipid; OliClinomel; Perismofven; Periven; Piascledine; Pluvio; Pulsalux; SMOFlipid; Soymen; Structolipid; ***Malaysia***: Kabiven†; ***Mex.***: Bano Coloide; Caltrate + S; Kabiven; Lipofundin MCT/LCT; Liposyn†; Piascledine; Prevefem Complex; Riban; Soyaloid Apruri; Soyaloid; Soydex; ***Mon.***: Evestrel Jour Nuit†; Evestrel Physio Profil†; ***Neth.***: Clinoleic; Kabiven; Lipofundin MCT/LCT†; Lipoplus; Numeta GE; Nutriflex Lipid; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Structolipid; Vitrimix KV†; ***Norw.***: Clinoleic; Kabiven; Lipidem; Numeta GE; Nutriflex Lipid; NuTRIflex Omega; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Vasolipid; ***NZ***: Clinoleic; Kabiven; OliClinomel; ***Philipp.***: Her Soy Plus; Kabiven; Livermin; ***Pol.***: Balneum Hermal Plus†; Clinoleic; Clinomel; Compleven†; Kabiven; Lipofundin MCT/LCT; Naturapia Menopauza; Piascledine; SMOFKabiven; SMOFlipid; ***Port.***: Banholeum Composto; Banholeum Gele; Clinoleic; Lipofundina MCT/LCT; Lipoplus; Nutribraun; Nutriplasmal†; OliClinomel; SMOFKabiven; SMOFlipid; Structolipid; Vitrimix; ***Rus.***: Kabiven (Кабивен); Lipofundin MCT/LCT (Липофундин МСТ/ЛСТ); Lipoplus (Липоплюс); Oliclinomel (ОлиКлиномель); Piascledine (Пиаскледин); SMOFlipid (СМОФлипид); ***S.Afr.***: Clinomel†; Lipofundin MCT/LCT†; ***Singapore***: Clinoleic; Kabiven; Lipofundin MCT/LCT; Pro-Gut; ***Spain***: Clinoleic; Fitogyn; Kabiven; Lipofundina MCT/LCT; Lipomix; Lipoplus; Nutriflex Lipid; NuTRIflex Omega; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Structolipid†; ***Swed.***: Clinoleic; Kabiven; Lipoplus; Numeta GE; Nutriflex Lipid; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Structolipid; Vasolipid; ***Switz.***: Antidry; Clinoleic; Lipofundin MCT/LCT; Lipoplus; Numeta; Nutriflex Lipid; OliClinomel†; Olimel; PeriOlimel; SmofKabiven; SMOFlipid; Structolipid; ***Thai.***: Cal-ups-D-Soy; Clinoleic; Kabiven; Lipidem; Lipofundin MCT/LCT; Nutriflex Lipid; OliClinomel; SMOFlipid; Vitrimix†; ***Turk.***: Clinoleic; Lipofundin MCT/LCT; Liposyn†; SMOFlipid; Vitrimix; ***UK***: Balneum Plus; Clinoleic; Emustil; Kabiven; Lipidem; Lipofundin MCT/LCT; Nutriflex Lipid; NuTRIflex Omega; OliClinomel; Phytolife Plus; Skin Perfecting Oil; SMOFlipid; Structolipid; Ymea; Zerozole†; ***Ukr.***: Kabiven (Кабивен); Lipofundin MCT/LCT (Липофундин МСТ/ЛСТ); SMOFlipid (СМОФлипид); ***USA***: Clinolipid; Liposyn II; Tucks; ***Venez.***: Lipofundin MCT/LCT; Maternavit.

Pharmacopoeial Preparations
USP 36: Lipid Injectable Emulsion.

Stannous Fluoride

Fluoruro estañoso; Stannosi Fluoridum; Фторид Олова.
Tin fluoride.
SnF_2=156.7
CAS — 7783-47-3.
ATC — A01AA04.
ATC Vet — QA01AA04.
UNII — 3FTR44B32Q.

Pharmacopoeias. In *US.*

USP 36: (Stannous Fluoride). A white crystalline powder. Freely soluble in water; practically insoluble in alcohol, in

chloroform, and in ether. pH of a freshly prepared 0.4% solution in water is between 2.8 and 3.5.

Stability. Aqueous solutions of stannous fluoride decompose within a few hours with the formation of a white precipitate; they slowly attack glass.

Profile

Stannous fluoride is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) for the prophylaxis of dental caries. Dental gels containing concentrations of stannous fluoride 0.4% are available for daily use. Higher concentrations have been applied under professional supervision. Stannous fluoride has also been used in dentifrices and mouth rinses.

Stannous fluoride has an unpleasant taste.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Gel-Kam; Gelstan; Perfect Solutions in Office Rinse†; *Fr.*: Emoform†; *Ital.*: Fluorigard Gel-Kam; Gel-Kam; Oral-B Pasta Dentifricia Denti e Gengive†; *UK*: Fluorigard Gel-Kam; *USA*: Gel Kam; Gel-Kam; Gel-Tin; Just for Kids; PerioMed; Stop.

Multi-ingredient Preparations. *Canad.*: Gel-Kam Dentinbloc; *Denm.*: Amerscan Stannous†; *Israel*: Meridol; *Ital.*: Actifluor.

Pharmacopoeial Preparations
USP 36: Stannous Fluoride Gel.

Starch

Almidón; Amidó; Amidon; Amidon de blé (wheat starch); Amidon de maïs (maize starch); Amidon de pomme de terre (potato starch); Amidon de riz (rice starch); Amidon prégélatinisé (pregelatinised starch); Amilo; Amylum; Amylum pregelificatum (pregelatinised starch); Bulvių krakmolas (potato starch); Burgonyakeményítő (potato starch); Búzakeményítő (wheat starch); Hidegenduzzadó keményítő (pregelatinised starch); Kukoricakeményítő (maize starch); Kukurūzų krakmolas (maize starch); Kviečių krakmolas (wheat starch); Maissitärkkelys (maize starch); Majsstärkelse (maize starch); Maydis amylum (maize starch); Oryzae amylum (rice starch); Perunatärkkelys (potato starch); Potatisstärkelse (potato starch); Pregelifikuotas krakmolas (pregelatinised starch); Pšeničný škrob (wheat starch); Riisitärkkelys (rice starch); Risstärkelse (rice starch); Rizskeményítő (rice starch); Ryžių krakmolas (rice starch); Škrob bramborový (potato starch); Škrob kukuřičný (maize starch); Škrob předbobtnalý (pregelatinised starch); Škrob rýžový (rice starch); Skrobia kukurydziana (maize starch); Skrobia pszeniczna (wheat starch); Skrobia ziemniaaczana (potato starch); Solani amylum (potato starch); Stärke; Tritici amylum (wheat starch); Vehnätärkkelys (wheat starch); Vetestärkelse (wheat starch); Крахмал.

CAS — 9005-25-8 (starch); 9005-82-7 (α-amylose); 9004-34-6 (β-amylose); 9037-22-3 (amylopectin).

UNII — O8232NY3SJ (corn starch); 8I089SAH3T (potato starch); 4DGK8B713S (rice starch); 245C3U704I (tapioca starch); 79QS2MG2LP (wheat starch).

Description. Starch consists of polysaccharide granules obtained from the caryopsis of maize, *Zea mays*, rice, *Oryza sativa*, wheat, *Triticum aestivum* (*T. vulgare*), from the tubers of potato, *Solanum tuberosum* from the seeds (peas) of *Pisum sativum*, or from the rhizomes of cassava, *Manihot utilissima*. Maize starch is also known as corn starch. Starch contains amylose and amylopectin, both polysaccharides based on α-glucose.

Pharmacopoeias. Some or all of the starches described are included in *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn*. Also in *USNF*.

Chin. and *Eur.* also include Pregelatinised Starch, *Eur.* includes Pregelatinised Hydroxypropyl Starch. *USNF* also includes Pregelatinized Starch, Modified Starch, Pregelatinized Modified Starch, and Pregelatinized Hydroxypropyl Starch. *US* includes Absorbable Dusting Powder and Topical Starch.

Ph. Eur. 8: (Maize Starch; Maydis Amylum). It is obtained from the caryopsis of *Zea mays*. It is a matt, white to slightly yellowish, very fine powder that creaks when pressed between the fingers. The presence of granules with cracks or irregularities on the edge is exceptional. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 4.0 to 7.0.

Ph. Eur. 8: (Pea Starch). It is obtained from the seeds of *Pisum sativum*. A white or almost white, very fine powder. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 5.0 to 8.0.

Ph. Eur. 8: (Potato Starch; Solani Amylum). It is obtained from the tuber of *Solanum tuberosum*. It is a very fine, white or almost white powder which creaks when pressed between the fingers. It does not contain starch grains of any other origin but may contain a minute quantity, if any, of fragments of the tissue of the original plant. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 5.0 to 8.0. Store in airtight containers.

Ph. Eur. 8: (Rice Starch; Oryzae Amylum). It is obtained from the caryopsis of *Oryza sativa*. It is a tasteless, very fine, white or almost white powder which creaks when pressed between the fingers. The presence of granules with cracks or irregularities on the edge is exceptional. Practically insoluble in cold water and in alcohol. Store in airtight containers.

Ph. Eur. 8: (Wheat Starch; Tritici Amylum). It is obtained from the caryopsis of *Triticum aestivum* (*T. vulgare*). It is a very fine, white or almost white powder which creaks when pressed between the fingers. It does not contain starch grains of any other origin but may contain a minute quantity, if any, of fragments of the tissue of the original plant. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 4.5 to 7.0. Store in airtight containers.

Ph. Eur. 8: (Pregelatinised Starch; Amylum Pregelificatum). It is prepared from maize starch, potato starch, or rice starch by mechanical processing in the presence of water, with or without heat, to rupture all or part of the starch granules, and subsequent drying. It contains no added substances but it may be modified to render it compressible and to improve its flow characteristics. It is a white or yellowish white powder that swells in cold water.

Ph. Eur. 8: (Starch, Hydroxypropyl; Amylum Hydroxypropylum). A partially substituted 2-hydroxypropylether of maize starch, potato starch, cassava starch, rice starch, or pea starch chemically modified by etherification with propylene oxide. In addition, this starch may be partially hydrolysed using acids or enzymes to obtain thinned starch with reduced viscosity. Mixing of starches from different botanical sources prior to chemical modification is not allowed. It contains 0.5% to 7.0% of hydroxypropyl groups. pH of a 20% suspension in carbon-dioxide-free water, after standing for 15 minutes, is 4.5 to 8.0. A white or slightly yellowish powder. Practically insoluble in cold water and in alcohol.

Ph. Eur. 8: (Starch, Hydroxypropyl, Pregelatinised; Amylum Hydroxypropylum Pregelificatum). It is prepared from hydroxypropyl starch by mechanical processing in the presence of water, with or without heat, to rupture all or part of the starch granules, and subsequent drying. It contains 0.5% to 7.0% of hydroxypropyl groups. pH of a 3.0% mixture in water is 4.5 to 8.0. A white or slightly yellowish powder.

BP 2014: (Tapioca Starch). It is obtained from the rhizomes of *Manihot utilissima*. It is a very fine powder which creaks when pressed between the fingers. Practically insoluble in cold water and in alcohol. Store in airtight containers.

The BP 2014 gives Cassava Starch as an approved synonym.

The BP 2014 directs that when starch is specified and the type is not indicated, Maize Starch, Potato Starch, Rice Starch, Wheat Starch, or in tropical countries where these are not available, Tapioca Starch may be supplied or used.

USNF 31: (Corn Starch). It consists of the starch granules separated from the mature grain of corn, *Zea mays* (Gramineae). Irregular, angular, white masses or fine powder. Is odourless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 4.0 to 7.0.

USNF 31: (Pea Starch). It is obtained from the seeds of *Pisum sativum*. A white or almost white, very fine powder. Practically insoluble in cold water and in alcohol.

USNF 31: (Potato Starch). It is obtained from the tuber of *Solanum tuberosum*. Irregular, angular, white masses or fine powder. Is odourless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 5.0 to 8.0.

USNF 31: (Rice Starch). It is obtained from the caryopsis of *Oryza sativa*. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 5.0 to 8.0.

USNF 31: (Tapioca Starch). Granules separated from the tubers of tapioca (cassava), *Manihot utilissima* (Euphorbiaceae). Irregular, angular, white to pale yellow masses or fine powder. Insoluble in cold water and in alcohol. A 20% slurry in water after 5 minutes of continuous agitation has a pH of 4.5 to 7.0.

USNF 31: (Wheat Starch). It is obtained from the caryopsis of *Triticum aestivum* (*T. vulgare*). Irregular, angular, white masses or fine powder. Is odourless and has a slight, characteristic taste. Insoluble in cold water and in alcohol. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 4.5 to 7.0.

USNF 31: (Hydroxypropyl Corn Starch). A partially substituted 2-hydroxypropylether obtained from corn starch by a chemical modification of etherification with propylene oxide. In addition, this starch may be partially hydrolysed using acids or enzymes to obtain thinned starch. It contains 2.0 to 7.0% of hydroxypropyl groups on the dried basis. pH of a 20% suspension in carbon-dioxide-free water, after standing for 15 minutes, is 4.5 to 8.0. A white or slightly yellowish powder. Practically insoluble in cold water and in alcohol.

USNF 31: (Hydroxypropyl Pea Starch). A partially substituted 2-hydroxypropylether obtained from pea starch by a chemical modification of etherification with propylene oxide. In addition, this starch may be partially hydrolysed using acids or enzymes to obtain thinned starch. It contains 2.0 to 7.0% of hydroxypropyl groups on the dried basis. pH of a 20% suspension in carbon-dioxide-free water, after standing for 15 minutes, is 4.5 to 8.0. A white or slightly yellowish powder. Practically insoluble in cold water and in alcohol.

USNF 31: (Hydroxypropyl Potato Starch). A partially substituted 2-hydroxypropylether obtained from potato starch by a chemical modification of etherification with propylene oxide. In addition, this starch may be partially hydrolysed using acids or enzymes to obtain thinned starch. It contains 2.0 to 7.0% of hydroxypropyl groups on the dried basis. pH of a 20% suspension in carbon-dioxide-free water, after standing for 15 minutes, is 4.5 to 8.0. A white or slightly yellowish powder. Practically insoluble in cold water and in alcohol.

USNF 31: (Pregelatinized Starch). It is starch that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. It may be modified to render it compressible and flowable.

USNF 31: (Modified Starch). It is starch modified by chemical means. Food starch may be acid-modified, bleached, oxidised, esterified, etherified, or treated enzymatically to change its functional properties. A 20% slurry in water, after 5 minutes stirring at a moderate rate, has a pH of 3.0 to 9.0.

USNF 31: (Pregelatinized Modified Starch). It is Modified Starch that has been chemically or mechanically processed, or both, to rupture all or part of the granules to produce a product that swells in cold water. Moderately coarse to fine, white to off-white powder. It is odourless and has a slight, characteristic taste. Slightly soluble to soluble in cold water; insoluble in alcohol.

USNF 31: (Pregelatinized Hydroxypropyl Corn Starch). Prepared from hydroxypropyl corn starch by mechanical processing in the presence of water, with or without heat, to rupture all or some of the starch granules, and subsequently dried. It contains 2.0% to 7.0% of hydroxypropyl groups on the dried basis. A white or slightly yellowish powder. It swells in water and produces a clear or translucent, viscous, colloidal mixture.

USNF 31: (Pregelatinized Hydroxypropyl Pea Starch). Prepared from hydroxypropyl pea starch by mechanical processing in the presence of water, with or without heat, to rupture all or some of the starch granules, and subsequently dried. It contains 2.0% to 7.0% of hydroxypropyl groups on the dried basis. A white or slightly yellowish powder. It swells in water and produces a clear or translucent, viscous, colloidal mixture.

USNF 31: (Pregelatinized Hydroxypropyl Potato Starch). Prepared from hydroxypropyl potato starch by mechanical processing in the presence of water, with or without heat, to rupture all or some of the starch granules, and subsequently dried. It contains 2.0% to 7.0% of hydroxypropyl groups on the dried basis. A white or slightly yellowish powder. It swells in water and produces a clear or translucent, viscous, colloidal mixture.

Uses and Administration

Starch is absorbent and is widely used in dusting powders, either alone or mixed with zinc oxide or other similar substances. Starch is used as a surgical glove powder, but such use has been discouraged (see p. 2096.2). It is incorporated in many tablets as a binder, diluent, or disintegrating agent. Pregelatinised starch is used similarly as a tablet binder.

Starch mucilage is given by mouth in the treatment of iodine poisoning; it has been used topically as a skin emollient.

Rice-based solutions may be used in the prevention and treatment of dehydration due to acute diarrhoeal diseases (p. 1805.2).

Glycogen storage disease type I. Type I glycogen storage disease is an autosomal recessive metabolic disorder in

which glucose-6-phosphatase is not expressed, resulting in hypoglycaemia due to lack of glucose production. Accumulation of glycogen and other metabolic derangements can lead to complications including renal impairment, hepatomegaly and hepatic adenoma, hyperuricaemia, hyperlipidaemias, and lactic acidosis. The condition has been successfully managed by continuous nocturnal nasogastric infusion of glucose and frequent daytime feedings. However, such a regimen requires good patient compliance and monitoring of the night-time infusions.[1]

As an alternative, a more standard diet together with uncooked corn starch suspensions prepared with tap water at room temperature and taken every 6 hours in doses of 1.75 to 2.5 g/kg have been reported[2] to be very satisfactory in maintaining normoglycaemia. In one infant, in whom starch was unsatisfactory, the lack of response was considered to be due to inadequate pancreatic amylase activity and although it was subsequently reported[3] that addition of a pancreatic enzyme concentrate had produced some improvement, the response was still inadequate to maintain normoglycaemia for more than 2 hours. It was considered that other amylase preparations should be identified for possible use in such patients. A small study of 7 young adults with glycogen storage disease type I found that a single dose of uncooked corn starch maintained plasma glucose concentrations for 7 hours in 5 of the patients.[4]

A long-term study of the effects of corn starch therapy found fewer complications among patients with near normal metabolic control and in those having started therapy at a younger age, but other factors appeared to be involved in the pathogenesis.[5] Corn starch therapy has nonetheless been reported to have improved proximal renal tubular dysfunction in 3 patients who had previously only had frequent daytime feeding as therapy. In 16 other patients previously treated with corn starch or glucose infusions, such renal dysfunction was not identified, and it was considered that the rapid response to therapy may explain why renal tubular dysfunction is not found more frequently in these patients.[6]

Because optimal metabolic control reduces the risk of developing long-term complications, an attempt has been made to define guidelines for long-term management of the disease.[7] Continuous nocturnal nasogastric feeding with a glucose or glucose polymer or a sucrose-free maltodextrin formula low in lactose may be introduced in very young infants. Uncooked corn starch should not be started in patients under 1 year of age as pancreatic amylase activity may be immature. Thereafter, since no significant differences in growth or biochemical parameters have been found between the use of nocturnal nasogastric infusions and uncooked corn starch overnight, corn starch may be started at a dose of 250 mg/kg and increased slowly to prevent adverse effects. It is recommended that the corn starch be mixed with water in a ratio of 1:2 and that an uncooked corn starch tolerance test be performed to establish the duration of the fasting period. The total dietary plan should aim to provide 60 to 65% of the total energy intake from carbohydrates, 10 to 15% from protein, and the remainder from fat, preferably vegetable oils with a high linoleic acid content. Lactose, fructose, and sucrose should be restricted. Drug therapy for metabolic complications may be necessary, such as allopurinol for hyperuricaemia, and bicarbonate for correction of lactic acidosis.[7]

For mention of the possible role of starch in the management of glycogen storage disease type V, see under Sucrose, below.

For a brief description of glycogen storage disease type II, see under Acid Alpha Glucosidase, p. 2428.1.

1. Goldberg T, Slonim AE. Nutrition therapy for hepatic glycogen storage diseases. *J Am Diet Assoc* 1993; 93: 1423–30.
2. Chen Y-T, *et al.* Cornstarch therapy in type I glycogen-storage disease. *N Engl J Med* 1984; 310: 171–5.
3. Chen Y-T, Sidbury JB. Cornstarch therapy in type I glycogen-storage disease. *N Engl J Med* 1984; 311: 128–9.
4. Wolfsdorf JI, Crigler JF. Cornstarch regimens for nocturnal treatment of young adults with type I glycogen storage disease. *Am J Clin Nutr* 1997; 65: 1507–11.
5. Weinstein DA, Wolfsdorf JI. Effect of continuous glucose therapy with uncooked cornstarch on the long-term clinical course of type Ia glycogen storage disease. *Eur J Pediatr* 2002; 161 (suppl): S35–S39.
6. Chen Y-T, *et al.* Amelioration of proximal renal tubular dysfunction in type I glycogen storage disease with dietary therapy. *N Engl J Med* 1990; 323: 590–3.
7. Rake JP, *et al.* Guidelines for management of glycogen storage disease type I - European study on glycogen storage disease type I (ESGSD I). *Eur J Pediatr* 2002; 161 (suppl): S112–S119.

Adverse Effects

Effects of cassava. In 1985 WHO added *malnutrition-related diabetes* (which included the type previously known as tropical diabetes) to its classification of diabetes mellitus.[1] Epidemiological evidence had suggested an association between fibrocalculous pancreatic diabetes (a subclass of malnutrition-related diabetes) and the consumption of cassava root (tapioca, manioc), which for many people living in tropical developing countries, where protein intake was low, was the main source of food energy.

Cassava root contains several cyanogenic substances and although food preparation and processing could reduce the cyanide content, there was the possibility that in persons with an inadequate protein intake, particularly if deficient in sulfur-containing amino acids which are involved in detoxification pathways, accumulation of cyanides might occur. WHO, however, did consider that further research was necessary to firmly establish any relation between this type of diabetes and high levels of cassava consumption. In a review that appeared in the following year[2] the cassava/malnutrition hypothesis was thought to be attractive, but unproven; also there was strong evidence against it being the only cause.

WHO deleted malnutrition-related diabetes from its 1998 report on the classification of diabetes.[3] Fibrocalculous pancreatic diabetes is now fibrocalculous pancreatopathy, a disease which may cause diabetic mellitus but is not considered a form of diabetes.

Konzo, an upper motor neurone disease characterised by spastic paraparesis,[4] and commonly associated with optic neuropathy,[5] has been reported to be caused by dietary exposure to cyanide after ingestion of cassava root. *Growth retardation* has also been associated with consumption of inadequately processed cassava.[6]

1. WHO. Diabetes mellitus: report of a WHO study group. *WHO Tech Rep Ser* 727 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_727.pdf (accessed 20/03/09)
2. Abu-Bakare A, *et al.* Tropical or malnutrition-related diabetes: a real syndrome? *Lancet* 1986; i: 1135–8.
3. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539–53.
4. Ernesto M, *et al.* Persistent konzo and cyanogen toxicity from cassava in northern Mozambique. *Acta Trop* 2002; 82: 357–62.
5. Mwanza J-C, *et al.* Neuro-ophthalmologic findings in konzo, an upper motor neuron disorder in Africa. *Eur J Ophthalmol* 2003; 13: 383–9.
6. Banea-Mayambu J-P, *et al.* Dietary cyanide from insufficiently processed cassava and growth retardation in children in the Democratic Republic of Congo (formerly Zaire). *Ann Trop Paediatr* 2000; 20: 34–40.

Glove powder. The use of starch glove powders by surgeons has resulted in contamination of surgical wounds by starch and in the development of complications such as inflammation, adhesions, and granulomatous lesions. In addition, glove starch powder may be a risk factor in the development of latex allergy, and may act as a vector for bacterial pathogens. Because of these risks, it has been proposed that the use of powder in latex gloves be banned,[1-5] a step which has been taken in some countries.[5]

1. Haglund U, Junghanns K, eds. Glove powder—the hazards which demand a ban. *Eur J Surg* 1997; 163 (suppl 579): 1–55.
2. AAAAI and ACAAI joint statement concerning the use of powdered and non-powdered natural latex gloves. *Ann Allergy Asthma Immunol* 1997; 79: 487.
3. Dave J, *et al.* Glove powder: implications for infection control. *J Hosp Infect* 1999; 42: 282–5.
4. Edlich RF, Reddy VR. A call to ban glove cornstarch. *Arch Surg* 2001; 136: 116.
5. Edlich RF, *et al.* Dangers of cornstarch powder on medical gloves: seeking a solution. *Ann Plast Surg* 2009; 63: 111–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Aptamil Feed Thickener; *Fr.*: Magic Mix; *India*: Bio-Sorb; *Mex.*: Panaline; *NZ*: Karicare Food Thickener.

Multi-ingredient Preparations. *Arg.*: Ninderm; Talquisedan; *Austral.*: Nucolox†; Summer's Eve Feminine; ZSC; *Canad.*: Bum-But-R; *Chile*: Talquisedan; *Fr.*: Poudre du Marcheur†; Supro; Trigopax; *India*: Derby Cool; Feel Chill†; *Indon.*: L-Bio; *Irl.*: Skin Clear†; *Israel*: Baby Paste†; *Ital.*: Glicerolax; Lenipasta; *NZ*: Lamisil Odor Eze†; *Port.*: Cuidaderma; *S.Afr.*: SB Universal Ointment†; *Turk.*: Alkagin; *UK*: Herbheal Ointment; Psorasolv; Skin Clear; *USA*: Balmex Baby; Desitin with Zinc Oxide; Diaparene Corn Starch; Mexsana; Paladin; Palomar E.

Pharmacopoeial Preparations
BP 2014: Compound Zinc Paste; Talc Dusting Powder;
USP 36: Absorbable Dusting Powder; Topical Starch.

Sucralose *(BANM)*

Sucralosa; Sucralosum; TGS; Trichlorogalactosucrose; Triclorogalactosucrosa; Сукралоза.

1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside.

$C_{12}H_{19}Cl_3O_8$=397.6

CAS — 56038-13-2.

UNII — 96K6UQ3ZD4.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sucralose). A white or almost white, crystalline powder. Freely soluble in water; soluble in anhydrous alcohol; slightly soluble in ethyl acetate.

USNF 31: (Sucralose). A white to off-white, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in ethyl acetate. Store in a cool, dry place at a temperature not exceeding 21 degrees.

Profile

Sucralose is used as a sweetening agent in foods, beverages, and pharmaceuticals. It has between about 300 and 1000 times the sweetening power of sucrose; this is not reduced by cooking. It has no food value and is noncariogenic.

References.
1. Anonymous. Sucralose—a new artificial sweetener. *Med Lett Drugs Ther* 1998; 40: 67–8.
2. Roberts A, *et al.* Sucralose metabolism and pharmacokinetics in man. *Food Chem Toxicol* 2000; 38 (suppl): S31–S41.
3. Grotz VL, Munro IC. An overview of the safety of sucralose. *Regul Toxicol Pharmacol* 2009; 55: 1–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Sugafor.

Sucrose

Azúcar; Azúcar de caña; Cane Sugar; Refined Sugar; Sacarosa; Saccharose; Saccharosum; Saccharum; Sacharosa; Sacharoze; Sacharoza; Sackaros; Sakkaroosi; Sucre; Sucrosum; Szacharóz; Zucker; Сахароза.

β-D-Fructofuranosyl-α-D-glucopyranoside.

$C_{12}H_{22}O_{11}$=342.3

CAS — 57-50-1.

UNII — C151H8M554 (sucrose); 8M707QY5GH (raw sugar).

Description. Sucrose is obtained from sugar-cane, *Saccharum officinarum* (Gramineae), sugar-beet, *Beta vulgaris* (Chenopodiaceae), and other sources.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *Viet.* Also in *USNF.*

Br. also contains Compressible Sugar.

Eur. also includes Sugar Spheres.

USNF also includes Compressible Sugar, Confectioner's Sugar, and Sugar Spheres.

Ph. Eur. 8: (Sucrose). A white or almost white, crystalline powder or shiny, colourless or white or almost white crystals. Very soluble in water; slightly soluble in alcohol; practically insoluble in dehydrated alcohol.

USNF 31: (Sucrose). A sugar obtained from *Saccharum officinarum* (Gramineae), *Beta vulgaris* (Chenopodiaceae), and other sources. White, crystalline powder or lustrous, dry, colourless or white crystals. Soluble 1 in 0.5 of water, 1 in 0.2 of boiling water, and 1 in 170 of alcohol; practically insoluble in dehydrated alcohol.

Incompatibility. Sucrose may be contaminated by traces of heavy metals or sulfites and this can lead to incompatibility with other ingredients when it is used as a pharmaceutical excipient. Syrup preserved with hydroxybenzoates has been reported to be incompatible with a range of compounds.

Uses and Administration

Sucrose, a disaccharide, is used as a sweetening agent. It is commonly used as household sugar. If the sweetness of sucrose is taken as 100, fructose has a value of about 173, glucose 74, maltose 32, galactose 32, and lactose 16.

Sucrose is used as a tablet excipient and lozenge basis, and as a suspending and viscosity-increasing agent. Syrups prepared from concentrated solutions of sucrose form the basis of many linctuses. Treacle (molasses), a byproduct of sugar production that contains sucrose and minerals, has also been used.

Sucrose 30% eye drops have been used as a hypertonic agent for clearing corneal oedema.

Cough. Sucrose syrups are used as demulcents in linctuses used for treating cough (p. 1651.2).

Diagnostic test for gastrointestinal damage. Sucrose is not absorbed from the healthy gastrointestinal tract. It has been proposed that the absorption of sucrose could be used as a diagnostic test of gastric damage.[1-3]

1. Sutherland LR, *et al.* A simple non-invasive marker of gastric damage: sucrose permeability. *Lancet* 1994; 343: 998–1000.
2. Meddings JB, *et al.* Sucrose permeability: a novel means of detecting gastroduodenal damage noninvasively. *Am J Ther* 1995; 2: 843–9.
3. Kawabata H, *et al.* Sucrose permeability as a means of detecting diseases of the upper digestive tract. *J Gastroenterol Hepatol* 1998; 13: 1002–6.

Gastrointestinal spasm. For mention of a beneficial effect of sucrose solution in infant colic, see p. 1807.1.

Glycogen storage disease type V. Glycogen storage disease type V (McArdle's disease) is a rare autosomal recessive disorder characterised by mutations in the gene for myophosphorylase, an enzyme essential for glycogenoly-

sis.[1,2] Patients present with exercise-induced pain, cramps, fatigue, and myoglobinuria which, if severe, can cause acute renal failure.[2] Low-dose creatine supplementation (60 mg/kg daily) produced modest benefits during ischaemic exercise testing, but higher doses (150 mg/kg daily) worsened symptoms.[2] Sucrose 75 g by mouth improved exercise tolerance in 12 patients in a randomised crossover study.[1] Uncooked corn starch, either alone or with sucrose, has been suggested as an alternative in order to avoid any pronounced increase in serum insulin;[3] but this has been rejected on the basis that the necessary rapid increase in blood glucose will not be produced.[4]

1. Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *N Engl J Med* 2003; 349: 2503–9.
2. Quinlivan R, *et al.* Pharmacological and nutritional treatment for McArdle's disease (glycogen storage disease type V). Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/07/08).
3. Gaglia JL, Wolfsdorf JI. Oral sucrose and exercise tolerance in McArdle's disease. *N Engl J Med* 2004; 350: 1575.
4. Vissing J, Haller RG. Oral sucrose and exercise tolerance in McArdle's disease. *N Engl J Med* 2004; 350: 1575–6.

Hiccup. Giving a teaspoon of dry granulated sugar resulted in the immediate cessation of hiccup in 19 of 20 patients;[1] 12 of the patients had suffered from hiccup for less than 6 hours but in the remaining 8 persistent hiccup had been present for 24 hours to 6 weeks. The effect may be due to stimulation of the pharynx. An early protocol for the treatment of intractable hiccup (p. 1046.3) suggests that swallowing dry granulated sugar is one of the first treatments that should be tried.

1. Engleman EG, *et al.* Granulated sugar as treatment for hiccups in conscious patients. *N Engl J Med* 1971; 285: 1489.

Pain. A systematic review[1] concluded that oral sucrose solutions could reduce physiological and behavioural indicators of stress and pain in neonates undergoing painful procedures although there had been some doubt expressed[2] over whether this indicated effective analgesia. The review[1] was unable to determine an optimal dose, but 1 mL of a 25% solution or 2 mL of a 50% solution has been reported to reduce crying time in premature[3] and full-term[4] infants, respectively, when given 2 minutes before heel-prick sampling. Similarly, in infants given intramuscular vaccines, 2 mL of a 75% sucrose solution by mouth reduced crying time,[5] and 2 mL of a 24% solution reduced pain scores;[6] 2 mL of oral sucrose 24% also reduced pain scores in premature infants undergoing eye examinations for retinopathy of prematurity.[7] One literature review[8] suggested that a dose of 500 mg sucrose provided effective analgesia for neonates. However, a randomised study found pacifiers (dummies) to have a better analgesic effect than 2 mL of a 30% sucrose solution; a synergistic effect was found with a combination of sucrose and pacifiers.[9] Another review[10] recommended that, along with a pacifier, 0.1 to 0.4 mL of a 24% sucrose solution be given to premature infants, and up to 2 mL be given to term infants. Others have recommended the use of 0.5 mL/kg of a 33% sucrose solution (about 170 mg/kg), stating that more dilute solutions carry a risk of bacterial contamination.[11] The route by which sucrose solution is given may also be important: a reduced pain response was only noted after intraoral doses; giving it via a nasogastric tube was ineffective.[12]

A study in preterm infants found that, while there were no differences on neurobehavioural developmental outcomes between infants given repeated sucrose analgesia or placebo, higher number of doses of sucrose predicted lower scores in motor development, vigour, alertness and orientation. The authors postulated that repeated stimulation by sucrose may interfere with normal functioning and maturation of the preterm infant's endogenous opiate system, and cautioned against the routine use of sucrose analgesia in this population.[13] For choice of analgesic in children, see p. 5.2.

1. Stevens B, *et al.* Sucrose for analgesia in newborn infants undergoing painful procedures. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 10/06/10).
2. Anonymous. Pacifiers, passive behaviour, and pain. *Lancet* 1992; 339: 275–6.
3. Ramenghi LA, *et al.* Reduction of pain response in premature infants using intraoral sucrose. *Arch Dis Child* 1996; 74: F126–F128.
4. Haouari N, *et al.* The analgesic effect of sucrose in full term infants: a randomised controlled trial. *BMJ* 1995; 310: 1498–1500.
5. Lewindon PJ, *et al.* Randomised controlled trial of sucrose by mouth for the relief of infant crying after immunisation. *Arch Dis Child* 1998; 78: 453–6.
6. Hatfield LA, *et al.* Analgesic properties of oral sucrose during routine immunizations at 2 and 4 months of age. *Pediatrics* 2008; 121: e327–e334. Available at: http://pediatrics.aappublications.org/cgi/reprint/121/2/e327 (accessed 03/03/09)
7. Gal P, *et al.* Efficacy of sucrose to reduce pain in premature infants during eye examinations for retinopathy of prematurity. *Ann Pharmacother* 2005; 39: 1029–33.
8. Masters-Harte LD, Abdel-Rahman SM. Sucrose analgesia for minor procedures in newborn infants. *Ann Pharmacother* 2001; 35: 947–52.
9. Carbajal R, *et al.* Randomised trial of analgesic effects of sucrose, glucose, and pacifiers in term neonates. *BMJ* 1999; 319: 1393–7.
10. Prince WL, *et al.* Treatment of neonatal pain without a gold standard: the case for caregiving interventions and sucrose administration. *Neonatal Netw* 2004; 23: 33–45.
11. Shann F. Suckling and sugar reduce pain in babies. *Lancet* 2007; 369: 721–3.
12. Ramenghi LA, *et al.* "Sucrose analgesia": absorptive mechanism or taste perception. *Arch Dis Child Fetal Neonatal Ed* 1999; 80: F146–F147.
13. Johnston CC, *et al.* Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age. *Pediatrics* 2002; 110: 523–8.

Wound healing. Sugar, either in the form of granulated sugar[1–3] or pastes composed of caster sugar and icing sugar,[4,7] has been used successfully in the treatment of wounds (p. 1690.1) including mediastinitis after cardiac surgery,[1,3] large abscesses and bed sores,[4,7] diabetic ulcers,[2,4] and recurrent bone infections after surgical debridement in patients with leprosy.[5] Debridement of the wound is believed to be due partly to the osmotic effect of sugar and partly to the mechanical cleansing action but it is not known how sugar stimulates granulation tissue to form.[4,7] Once granulation tissue is well established and the wound is shrinking, an alternative wound preparation, such as an alginate, hydrocolloid, or hydrogel, should be used as sugar pastes cause bleeding.[8] Sugar is also effective at deodorising malodorous wounds. The use of the combined caster and icing sugar pastes, of which details of the formulas used are provided in the original publications,[4,7] has been advocated as a way to overcome the problems of possible non-sterility and contamination of commercial granulated sugar.[4,7]

Honey (p. 2072.2) has been used similarly.

1. Trouillet JL, *et al.* Use of granulated sugar in treatment of open mediastinitis after cardiac surgery. *Lancet* 1985; ii: 180–4.
2. Quatraro A, *et al.* Sugar and wound healing. *Lancet* 1985; ii: 664.
3. De Feo M, *et al.* Treatment of recurrent postoperative mediastinitis with granulated sugar. *J Cardiovasc Surg* 2000; 41: 715–19.
4. Kilic A. Healing of diabetic ulcers with granulated sugar. *Plast Reconstr Surg* 2001; 108: 585.
5. Grauwin MY, *et al.* Comment guérir les ostéites et ostéo-arthrites des extrémités des anciens malades de la lèpre par le sucre cristallisé alimentaire? *Acta Leprol* 1999; 11: 147–52.
6. Gordon H, *et al.* Sugar and wound healing. *Lancet* 1985; ii: 663–4.
7. Middleton KR, Seal D. Sugar as an aid to wound healing. *Pharm J* 1985; 235: 757–8.
8. Seal DV, Middleton K. Healing of cavity wounds with sugar. *Lancet* 1991; 338: 571–2.

Adverse Effects and Precautions

Sucrose consumption increases the incidence of dental caries.

Sucrose use should be avoided in patients with the glucose-galactose malabsorption syndrome, fructose intolerance, or sucrase-isomaltase deficiency. The intake of sucrose from dietary and other sources must be controlled in patients with diabetes mellitus.

Dietary sugar. The Panel on Dietary Sugars reviewed the evidence relating to sugars in the diet and the health of the population in the UK.[1]

No evidence was found that the consumption of most sugars naturally incorporated into the cellular structure of foods (intrinsic sugars) represented a threat to health and consideration was therefore mainly directed towards the dietary use of sugars not so incorporated (extrinsic sugars), of which sucrose was the principal non-milk extrinsic sugar.

There was extensive evidence suggesting that sugars were the most important dietary factor in the cause of dental caries and it was recommended that consumption of non-milk extrinsic sugars should be decreased.

It was considered that dietary sugars may contribute to the development of obesity, a condition which plays an important part in the aetiology of many diseases. For the majority of the population, who had normal plasma lipids and normal glucose tolerance, the consumption of sugars within the present range carried no special metabolic risks but those persons consuming more than about 200 g daily should replace the excess with starch. It was, however, recommended that those with special medical problems such as diabetes or hypertriglyceridaemia should restrict non-milk extrinsic sugar to less than about 20 to 50 g daily unless otherwise instructed by their own physician or dietitian. It was also concluded that current consumption of sugars, particularly sucrose, played no direct causal role in the development of cardiovascular (atherosclerotic coronary, peripheral, or cerebral vascular) disease, essential hypertension, or diabetes mellitus, and also had no significant specific effects on behaviour or psychological function. Although links between sucrose intake and certain other diseases (such as colorectal cancer, renal and biliary calculi, and Crohn's disease) had been proposed it was not felt that the evidence was adequate to justify any general dietary recommendations.

The conclusions of a joint FAO/WHO consultation on carbohydrates in human nutrition[2] were broadly in agreement with the above. However, they noted that the terms intrinsic and extrinsic sugars had not gained wide acceptance, either in the UK or other countries in the world, and they recommended against the use of these terms. In the USA, the term added sugars has also been used to describe sugars and syrups which are added to foods during processing or preparation. Guidance on dietary intakes issued by the American Food and Nutrition Board suggested a maximum intake of 25% of energy from added sugars.[3] The American Heart Association[4] has also recommended a reduced intake of added sugars, and suggested a specific upper limit; most American women should eat or drink no more than 100 calories daily from added sugars, and no more than 150 calories daily from added sugars for most American men.

1. DoH. Dietary sugars and human disease: report of the panel on dietary sugars of the committee on medical aspects of food policy. *Report on health and social subjects 37*. London: HMSO, 1989.
2. FAO/WHO. *Carbohydrates in human nutrition: report of a joint FAO/WHO expert consultation. FAO Food and Nutrition 66*. Rome: Food and Agriculture Organization of the United Nations, 1998. Also available at: http://www.fao.org/docrep/W8079E/w8079e00.htm (accessed 20/03/09)
3. *et al.*. Dietary Reference Intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academy Press, 2005. Also available at: http://books.nap.edu/openbook.php?record_id=10490&page=R1 (accessed 12/02/09)
4. Johnson RK, *et al.* American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation* 2009; 120: 1011–20. Also available at: http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192627 (accessed 11/02/10)

Effects on the kidneys. Acute renal failure with severe hyponatraemia has followed the use of granulated sugar to treat an infected pneumonectomy wound cavity.[1] It was noted that intravenous sucrose had long been known to be nephrotoxic in both *animal* models and man and that mild renal insufficiency before sucrose intoxication might have contributed to the nephrosis. Others, however, considered that the nephrotoxicity might have been caused by gentamicin, a solution of which had been used to irrigate the cavity before packing the wound.[2] Intravenous immunoglobulin preparations containing sucrose (as a stabilising agent) have also caused acute renal failure.[3,4]

1. Debure A, *et al.* Acute renal failure after use of granulated sugar in deep infected wound. *Lancet* 1987; i: 1034–5.
2. Archer H, *et al.* Toxicity of topical sugar. *Lancet* 1987; i: 1485–6.
3. Ahsan N, *et al.* Intravenous immunoglobulin-induced osmotic nephrosis. *Arch Intern Med* 1994; 154: 1985–7.
4. Zhang R, Szerlip HM. Reemergence of sucrose nephropathy: acute renal failure caused by high-dose intravenous immune globulin therapy. *South Med J* 2000; 93: 901–4.

Pharmacokinetics

Sucrose is hydrolysed in the small intestine by the enzyme sucrase to glucose and fructose, which are then absorbed. Sucrose is excreted unchanged in the urine when given intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Gelodiet; Pacidol.

Multi-ingredient Preparations. *Arg.*: Semble; *Austral.*: Nyal Chesty Cough; *Fr.*: Adiaril; Alhydrate†; Hydrigoz†; Picolite; *Hung.*: Bittner; *India*: A2-2; Energy Plus; Lycosta; *Irl.*: Rehidrat†; Venos Expectorant; *Jpn*: U-Pasta; *Philipp.*: Cholyte Plus With Zinc; Orhydrate†; SportsAde; *S.Afr.*: Emetrol; Rehidrat; *Thai.*: D-Lyte; *UK*: Honey & Molasses; Venos Cough Mixture; Venos Expectorant.

Pharmacopoeial Preparations

BP 2014: Compressible Sugar; Syrup;
Ph. Eur.: Sugar Spheres;
USNF 31: Compressible Sugar; Confectioner's Sugar; Sugar Spheres; Syrup.

Sucrose Polyesters

Sacarosa, poliésteres de la; Полиэфиры Сахарозы.

Profile

A sucrose polyester that is a mixture of hexa-, hepta-, and octa-fatty acid esters of sucrose is used as a nondigestible fat substitute by the food industry. Fat substitutes have been promoted as part of a strategy to reduce fat and calories in the diet to aid body-weight control.

Possible adverse effects of sucrose polyesters are flatulence, anal leakage, abdominal cramps, and loose bowel movements. They may also reduce the absorption of fat-soluble vitamins.

References.

1. Cotton JR, *et al.* Replacement of dietary fat with sucrose polyester: effects on energy intake and appetite control in non-obese males. *Am J Clin Nutr* 1996; 63: 891–6.
2. Goldman P. Olestra: assessing its potential to interact with drugs in the gastrointestinal tract. *Clin Pharmacol Ther* 1997; 61: 613–18.
3. Cheskin LJ, *et al.* Gastrointestinal symptoms following consumption of olestra or regular triglyceride potato chips: a controlled comparison. *JAMA* 1998; 279: 150–2.

The symbol † denotes a preparation no longer actively marketed

4. Sandler RS, *et al.* Gastrointestinal symptoms in 3181 volunteers ingesting snack foods containing olestra or triglycerides. *Ann Intern Med* 1999; 130: 253–61.
5. Bray GA, *et al.* A 9-mo randomized clinical trial comparing fat-substituted and fat-reduced diets in healthy obese men: the Ole Study. *Am J Clin Nutr* 2002; 76: 928–34.

Sunflower Oil

Aceite de girasol; Auringonkukkaöljy; Helianthi Annui Oleum; Helianthi Oleum; Huile de Tournesol; Napraforgóolaj; Olej słonecznikowy; Oleum Helianthi; Saulėgrąžų aliejus; Slunečnicový olej; Solrosolja; Sonnenblumenöl; Sunflowerseed Oil; Tournesol; huile de; Подсолнечное Масло.

ATC Herb — HA06AX5005 (Helianthus annuus: seed oil); HD02WB5003 (Helianthus annuus: oil).

UNII — 3W1JG795YI.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sunflower Oil, Refined; Helianthi Annui Oleum Raffinatum). The fatty oil obtained from the seeds of *Helianthus annuus* by mechanical expression or by extraction and then refined. A suitable antoxidant may be added. A clear, light yellow liquid. Practically insoluble in water and in alcohol; miscible with petroleum spirit (b.p.: 40 degrees to 60 degrees). Store in well-filled airtight containers. Protect from light.

USNF 31: (Sunflower Oil). A refined fixed oil obtained from the seeds of the sunflower plant *Helianthus annuus* (Asteraceae alt. Compositae). Specific gravity between 0.914 and 0.924 at 20 degrees. Store in airtight containers. Protect from light.

Profile

Sunflower oil is the fixed oil expressed from the fruits of *Helianthus annuus*. It is used as a salad oil and in pharmaceutical preparations. It is rich in linoleic acid (p. 2509.2).

Multiple sclerosis. As discussed on p. 996.3, the role of dietary lipids in multiple sclerosis remains to be proven,[1] although many patients modify their diets and take supplements of sunflower and other oils. One study showed a reduction in severity and duration of relapse in patients taking linoleic acid supplements (as sunflower oil).[2] Another[3] reported benefit in patients who limited their intake of dietary saturated fatty acids and supplemented their diet with polyunsaturated fatty acids. A systematic review[4] of the relationship between dietary interventions (including linoleic acid given as sunflower oils) and multiple sclerosis concluded that there was insufficient evidence to determine their benefits or risks.

1. Anonymous. Lipids and multiple sclerosis. *Lancet* 1990; 336: 25–6.
2. Millar JHD, *et al.* Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. *BMJ* 1973; 1: 765–8.
3. Swank RL, Dugan BB. Effect of low saturated fat diet in early and late cases of multiple sclerosis. *Lancet* 1990; 336: 37–9.
4. Farinotti M, *et al.* Dietary interventions for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/04/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Singapore*: Lubrex†.

Multi-ingredient Preparations. *Austria*: Pelsana Med; Piniment; *Fr.*: Menolistica; Oropur; Trigopax; *Ger.*: Kneipp Arnika Salbe S; *Hong Kong*: Sanjukei Panax Ginseng; *Hung.*: Pelsano Med; Pelsano Med; *India*: Alovit-AF; *Ital.*: DHA; *NZ*: Snorenz; *Philipp.*: Nutri-Aid; *Singapore*: Snoreeze; *Switz.*: Huile de millepertuis A. Vogel (huile de St. Jean); Pelsano; Pelsano; *Turk.*: Snoreless; *UK*: Goodnight StopSnore; Snor-Away.

Tagatose

D-lyxo-hexulose; D-Tagatose; Tagatosum; Tagatoza; Таратоза.

$C_6H_{12}O_6$=180.2.

CAS — 87-81-0 (tagatose); 17598-81-1 (D-tagatose).

UNII — T7A20Y888Y.

Pharmacopoeias. In *USNF.*

USNF 31: (Tagatose). Tagatose is a ketohexose, an epimer of fructose inverted at C-4. It is obtained from galactose by isomerisation under alkaline conditions in the presence of calcium. White or almost white crystals, having a sweet taste. Very soluble in water; very slightly soluble in alcohol.

Profile

Tagatose is a naturally occurring monosaccharide, produced commercially from lactose. It is 92% as sweet as sucrose, but contains fewer calories. It may be used as a sweetener in foods, beverages, toothpaste, mouthwashes, and medicines.

Threonine *(BAN, USAN, rINN)*

β-Methylserine; L-Thr; Threonin; L-Threonine; Threonine; Threoninum; Treonina; Treonini; Treonin; Treonina; Treoninas; Треонин.

L-2-Amino-3-hydroxybutyric acid.

$C_4H_9NO_3$=119.1.

CAS — 72-19-5 (L-threonine); 80-68-2 (DL-threonine).

UNII — 2ZD004190S.

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

Ph. Eur. 8: (Threonine). Fermentation product, extract or hydrolysate of protein. A white or almost white, crystalline powder or colourless crystals. Soluble in water; practically insoluble in alcohol. A 2.5% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 36: (Threonine). White, odourless crystals. Freely soluble in water; insoluble in dehydrated alcohol, in chloroform, and in ether. pH of a 5% solution in water is between 5.0 and 6.5.

Profile

Threonine is an amino acid that is an essential constituent of the diet. It is used as a dietary supplement.

Threonine has been investigated for the treatment of various spastic disorders.

DL-Threonine has been used in topical preparations for skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Cicatrex Biotic; *Austral.*: Cicatrin†; *Braz.*: Cicatrene; *Irl.*: Cicatrin†; *Ital.*: Cicatrene; *Port.*: Cicatrin; *Rus.*: Biotredin (Биотредин); *S.Afr.*: Cicatrin†; *Switz.*: Cicatrex; *Thai.*: Genquin.

Tricaprylin

AC-1202; Caprylic Acid Triglyceride; Caprylic Triglyceride; Caprylidene; Glycerin Tricaprylate; 1,2,3-Tricapryloylglycerol. Glyceryl trioctanoate; Propane-1,2,3-triyl trioctanoate.

$C_{27}H_{50}O_6$=470.7.

CAS — 538-23-8.

UNII — 6P92858988.

NOTE. The name Ketasyn has been used as a trade mark for tricaprylin.

Profile

Tricaprylin is a medium-chain triglyceride which is metabolised to ketone bodies, providing an alternative energy substrate to glucose; it elevates serum-ketone levels and is promoted for use in the clinical dietary management of patients with Alzheimer's disease. It has been supplied as a powder formulation in 10 or 40 g sachets containing 5 or 20 g of tricaprylin, respectively. It is given as an oral dose of 20 g tricaprylin daily, preferably with or after a full meal (usually breakfast or lunch). The main adverse effects are gastrointestinal such as diarrhoea, flatulence, or dyspepsia. A starting dose of 5 g tricaprylin daily, increased gradually over 7 days as tolerated, may minimise these effects. It should be used with caution in patients at risk of ketoacidosis.

References.

1. Costantini LC, *et al.* Hypometabolism as a therapeutic target in Alzheimer's disease. *BMC Neurosci* 2008; 9 (suppl 2): S16.
2. Henderson ST, *et al.* Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond)* 2009; 6: 31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Axona.

Tuna-liver Oil

Tunny-liver Oil.

Profile

Tuna-liver oil is a source of vitamin D (p. 2112.3) and vitamin A (below). It also contains several essential fatty acids. It is used, similarly to cod-liver oil (p. 2056.3), as a nutritional supplement and has been used in skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Femme Plus†.

Tyrosine *(BAN, USAN, rINN)*

Tirosina; Tirozin; Tirozinas; Tyr; Tyroslini; Tyrosin; L-Tyrosine; Tyrosinum; Tyrozyna; Y; Тирозин.

L-2-Amino-3-(4-hydroxyphenyl)propionic acid.

$C_9H_{11}NO_3$=181.2.

CAS — 60-18-4.

UNII — 42HK56048U.

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

Ph. Eur. 8: (Tyrosine). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Tyrosine). White, odourless crystals or crystalline powder. Very slightly soluble in water; insoluble in alcohol and in ether.

Profile

Tyrosine is an aromatic non-essential amino acid. It is used as a dietary supplement. The sodium salt has also been used.

Phenylketonuria. Tyrosine was not an effective alternative to a diet low in phenylalanine in patients with phenylketonuria, see under Amino Acid Metabolic Disorders, p. 2042.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Aussie Tan Pre-Tan†; PM LifePro Max for Men; PM LifePro Max for Women; Prosense for Men†; Prosense for Women†; Zellulean with Escin†; *Fr.*: Dynabiane; Fibromyalgine Fort; Fibromyalgine; Phytozac; Silinovea; *India*: Ipreg; Placentrex; *Indon.*: Femosa; *Port.*: Rilastil Dermo Solar; *Ukr.*: Stifimol (Стифимол); *USA*: Adrenoid.

Valine *(BAN, USAN, rINN)*

α-Aminoisovaleric Acid; V; Val; Vallini; Valin; Valina; Valinas; L-Valine; Valinum; Валин.

(*S*)-2-Amino-3-methylbutanoic acid.

$C_5H_{11}NO_2$=117.1.

CAS — 72-18-4.

UNII — HG1889YR57.

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

Ph. Eur. 8: (Valine). Fermentation product, extract or hydrolysate of protein. A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Valine). White, odourless crystals. Soluble in water; practically insoluble in alcohol, in acetone, and in ether. pH of a 5% solution in water is between 5.5 and 7.0.

Profile

Valine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Revitalose; *Ger.*: Falkamin; *Ital.*: Isobranch; Isoram; Sargenor Sport†.

Vitamin A *(USAN)*

Antixerophthalmic Vitamin; A-vitamiini; A-vitamin; Axerophthiolum; Oleovitamin A; Retinol (BAN); Retinol (rINN); Retinol; Retinolum; Vitamin A Alcohol; Vitamina A; Vitaminas A; Vitamine A; Vitaminum A; Witamina A; Ретинол.

15-Apo-β-caroten-15-ol; 3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraen-1-ol.

$C_{20}H_{30}O$=286.5.

CAS — 68-26-8.

ATC — A11CA01; D10AD02; R01AX02; S01XA02.

ATC Vet — QA11CA01; QD10AD02; QR01AX02; QS01XA02.

UNII — 81G40H8B0T (vitamin A); G2SH0XKK91 (retinol).

Description. Vitamin A is generally used in the form of esters, such as the acetate, palmitate, and propionate.

Vitamin A Acetate. Retinol Acetate; Retinyl Acetate; $C_{22}H_{32}O_2$ = 328.5; CAS — 127-47-9

Vitamin A Palmitate. Retinol Palmitate; Retinyl Palmitate; $C_{36}H_{60}O_2$ = 524.9; CAS — 79-81-2

Vitamin A Propionate. Retinol Propionate; Retinyl Propionate; $C_{23}H_{34}O_2$ = 342.5; CAS — 7069-42-3.

Pharmacopoeias. In *Eur.* (see p. vii), *US*, and *Viet.*, which permit retinol or its esters.

Chin. includes a monograph for the acetate. *Jpn* includes monographs for the acetate and the palmitate.

Br. includes a monograph for a natural ester concentrate.

Eur. also includes monographs for synthetic concentrates in an oily form, a powder form, and a solubilisate/emulsion.

Int. includes an oily concentrated form.

The BP 2014 states that the term 'Retinol' is used within BP titles for preparations containing synthetic ester(s) and the term 'Vitamin A' within the BP title for the preparation containing material of natural origin.

Ph. Eur. 8: (Vitamin A). Under the name Vitamin A are included a number of substances of very similar structure (including (Z)-isomers) found in animal tissues and possessing similar activity. The principal and biologically most active substance is all-(*E*) retinol.

Vitamin A is generally used in the form of esters such as the acetate, propionate, and palmitate. Synthetic retinol ester refers to an ester (acetate, propionate, or palmitate) or a mixture of synthetic retinol esters.

Retinol acetate occurs as pale yellow crystals. M.p. about 60 degrees; once melted it tends to yield a supercooled melt. Retinol propionate occurs as a reddish-brown oily liquid. Retinol palmitate occurs as a fat-like, light yellow solid, or as a yellow oily liquid, if melted. M.p. about 26 degrees. All retinol esters are practically insoluble in water; soluble or partly soluble in dehydrated alcohol; miscible with organic solvents.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used should be protected by an atmosphere of inert gas.

Ph. Eur. 8: (Vitamin A Concentrate (Oily Form), Synthetic; Vitaminum A Densatum Oleosum; Synthetic Retinol Concentrate (Oily Form) BP 2014). It is prepared from synthetic retinol ester as is or by dilution with a suitable vegetable oil. It contains not less than 500 000 units of vitamin A per g. It is a yellow or brownish-yellow, oily liquid; practically insoluble in water; soluble or partly soluble in dehydrated alcohol; miscible with organic solvents. Partial crystallisation may occur in highly concentrated solutions.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

Ph. Eur. 8: (Vitamin A Concentrate (Powder Form), Synthetic; Vitaminum A Pulvis; Synthetic Retinol Concentrate (Powder Form) BP 2014). It is obtained by dispersing a synthetic retinol ester in a matrix of gelatin or acacia or other suitable material. It contains not less than 250 000 units of vitamin A per g. It is a yellowish powder usually in the form of particles of almost uniform size. Practically insoluble in water or may swell or form an emulsion, depending on formulation.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

Ph. Eur. 8: (Vitamin A Concentrate (Solubilisate/Emulsion), Synthetic; Vitaminum A in Aqua Dispergibile; Synthetic Retinol Concentrate, Solubilisate/Emulsion BP 2014). It is a liquid form (water is generally used as solvent) of synthetic retinol ester and a suitable solubiliser. It contains not less than 100 000 units of vitamin A per g. It is a yellow or yellowish liquid of variable opalescence and viscosity. Highly concentrated solutions may become cloudy at low temperatures or take the form of a gel. A mixture of 1 g with 10 mL of water previously warmed to 50 degrees gives after cooling to 20 degrees, a uniform, slightly opalescent and slightly yellow dispersion.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

BP 2014: (Natural Vitamin A Ester Concentrate). It consists of a natural ester or a mixture of natural esters of retinol or of a solution of the ester or mixture of esters in arachis oil or other suitable vegetable oil. It contains not less than 485 000 units of vitamin A per g. It is a yellow oil or a mixture of oil and crystalline material, with a faint odour. Practically insoluble in water; soluble or partly soluble in alcohol; miscible with chloroform, with ether, and with petroleum spirit. Store in airtight containers at 8 degrees to 15 degrees. Protect from light.

USP 36: (Vitamin A). It may consist of retinol or its esters formed from edible fatty acids, principally acetic and palmitic acids. In liquid form, it is a light yellow to red oil that may solidify upon refrigeration. In solid form, has the appearance of any diluent that has been added. It may be practically odourless or may have a mild fishy odour but no rancid odour or taste. It is unstable in air and light. In liquid form, it is insoluble in water and in glycerol; soluble in dehydrated alcohol and in vegetable oils; very soluble in chloroform and in ether. In solid form, may be dispersible in water. Store in airtight containers, preferably under an atmosphere of inert gas. Protect from light.

Units

The International Standards for vitamin A and for provitamin A were discontinued in 1954 and 1956 respectively but the International units for these substances have continued to be widely used. In 1960–1, the WHO Expert Committee on Biological Standardization stated that the International unit for vitamin A is equivalent to the activity of 0.000344 mg of pure all-*trans* vitamin A acetate and the International unit for provitamin A is equivalent to the activity of 0.0006 mg of pure all-*trans* β-carotene.

The activity of one International unit is contained in 0.0003 mg of all-*trans* retinol, in 0.00055 mg of all-*trans* retinol palmitate, and in 0.000359 mg of all-*trans* retinol propionate.

The USP 36 defines 1 USP unit as equal to the biological activity of 0.0003 mg of the all-*trans* isomer of retinol, and is equivalent to the International unit.

Vitamin A activity in foods is currently expressed in terms of retinol equivalents: 1 retinol equivalent is defined as 1 microgram of all-*trans* retinol, 6 micrograms of all-*trans* beta carotene, or 12 micrograms of other provitamin A carotenoids.

Uses and Administration

Vitamin A, a fat-soluble vitamin, is essential for growth, for the development and maintenance of epithelial tissue, and for vision, particularly in dim light. Vitamin A deficiency develops when the dietary intake is inadequate and is seen more frequently in young children than in adults. It is rare in developed countries but remains a major problem in many developing countries. Prolonged deficiency leads to xerophthalmia or 'dry eye', the initial symptom of which is night blindness which may progress to severe eye lesions and blindness. Other symptoms include changes in the skin and mucous membranes.

Vitamin A is used in the treatment and prevention of vitamin A deficiency. It may be given orally in an oil- or water-based form, the oil-based generally being the preferred type. It can also be given by intramuscular injection of a water-miscible form; oil-miscible preparations of vitamin A are poorly absorbed from injection sites after intramuscular injection and are not usually given by this route. For further details concerning vitamin A supplementation, including doses for the treatment and prophylaxis of xerophthalmia, see p. 2101.1.

Vitamin A supplements are often given to patients with primary biliary cirrhosis or chronic cholestatic liver disease as deficiencies are common in these disorders. An intramuscular dose of 100 000 units every 2 to 4 months has been suggested. For doses in children, see below.

Vitamins A and D have been used together in creams or ointments in the treatment of minor skin disorders including abrasions. Vitamin A has also been used alone to treat various skin disorders including acne and psoriasis. It has been tried in patients with retinitis pigmentosa to retard the decline in retinal function.

Administration in children. Vitamin A supplementation may be required in children with cholestatic liver disease; the *BNFC* suggests an intramuscular dose of 50 000 units once monthly in neonates and children aged up to 1 year to prevent deficiency in complete biliary obstruction.

For further details concerning vitamin A supplementation in deficiency states, see below.

Deficiency states. Vitamin A deficiency is relatively rare in developed countries and is usually only seen in certain medical conditions such as biliary cirrhosis or cholestatic jaundice. However, it is a continuing problem in many developing countries and children appear to be particularly vulnerable.

In **developing countries** where dietary intake is often less than desirable, infections such as measles, acute respiratory diseases, and diarrhoea can be major precipitating factors of vitamin A deficiency. Thus WHO have targeted elimination of vitamin A deficiency as an important strategy in child health,[1,2] and as part of the Expanded Programme on Immunization. They recommend the use of vitamin A supplements in the treatment of vitamin A deficiency and to prevent vitamin A deficiency where the periodic use of supplements is determined to be the most feasible and effective method of improving vitamin A status.

- In *universal distribution programmes*,[2,3] supplemental doses are given to all children up to the age of 5 at a dose of 200 000 units every 4 to 6 months, with infants between the ages of 6 and 12 months receiving half this dose. Infants aged less than 6 months may receive 50 000 units if they are not breast fed or if they are breast fed and their mothers have not received supplemental vitamin A. If clinical signs of vitamin A deficiency are evident at the time of routine supplementation, treatment should be given as described under Xerophthalmia, p. 2101.1. Mothers should receive 200 000 units within 6 weeks of delivery of a child.
- *Targeted distribution programmes* involve vitamin A supplementation to children and pregnant women in specific high-risk areas.[2] Doses used in children are similar to those used in universal programmes, but doses used in pregnant women should not exceed 10 000 units daily, or 25 000 units weekly.[2]

A number of studies have indicated that general supplementation with vitamin A decreases both mortality rates and morbidity among children in developing countries with a high prevalence of vitamin A deficiency.[4-7] Although not all studies have confirmed these findings,[8,9] two meta-analyses concur that the effect is likely to be genuine especially as regards measles infection.[10,11] (see Measles, p. 2100.3) and researchers and commentators have agreed that overall improvement of vitamin A status is worthwhile and necessary.[12-14] A study in children given half the dose of vitamin A recommended by WHO found that it provided equally good or better protection against mortality, but not against morbidity.[15] Supplementation with vitamin A 23 300 units weekly, or the equivalent amount of betacarotene, in women of child-bearing age reduced pregnancy-related mortality.[16] Studies have also evaluated mortality specifically in infants less than 6 months of age with varying results. Some have found no overall benefit on early infant mortality;[17,18] one study reported a tendency for the relative risk of mortality to increase with improved nutritional status.[17] A systematic review[19] also failed to find evidence of benefit. No sustained benefit was seen on vitamin A status or morbidity beyond the age of 6 months, in infants receiving vitamin A supplements with immunisation at 6, 10, and 14 weeks.[20] Another study in west Africa, noted variations in mortality rate between the sexes and according to the season in which the supplement was given, with an increased mortality in girls supplemented in the rainy season but a reduced mortality among boys supplemented in the dry season.[18] Others have reported overall decreases in mortality at 6 months[21] and 1 year[22] of age. A study in vitamin-A-deficient children has demonstrated abnormalities in T-cell subsets which are corrected by vitamin A supplementation,[23] and it has been proposed that the apparent effects of vitamin A on morbidity and mortality may be due to modulation of immune function (see also Effects on the Immune System, p. 2101.3). Discrepancies in results could be explained by inherent differences between the populations being studied, such as vitamin A deficiency status and infant mortality rates.[24]

In **other countries** in which vitamin A deficiency is not widespread some form of supplementation may still be considered. In the UK, the *BNFC* suggests the following oral doses, with or after food, according to age:

- neonates and infants up to 1 year: 5000 units daily
- 1 to 18 years: 10 000 units daily

Higher doses may be used initially for the treatment of severe deficiency. Preterm infants have low vitamin A status at birth, which may increase their risk of developing chronic lung disease.[25] A meta-analysis of studies in low birthweight infants found that vitamin A supplementation was associated with a reduced requirement for oxygen at 36 weeks postmenstrual age.[25] While studies of vitamin A supplementation to prevent chronic lung disease in very low birth-weight infants have had conflicting results,[26,27] some have commented that differences in patient population, postnatal therapies, and dosage of vitamin A could explain these discrepancies, and consider optimal supplementation necessary.[28] Others have called for further studies in preterm infants to define optimal dosage and mode of delivery of vitamin A; research should include quantification of hepatic stores, assessment of retinal function, and long-term clinical outcome.[29]

1. Potter AR. Reducing vitamin A deficiency: could save the eyesight and lives of countless children. *BMJ* 1997; 314: 317–18.
2. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia.* 2nd ed. Geneva: WHO, 1997.
3. WHO. Integration of vitamin A supplementation with immunization. *Wkly Epidem Rec* 1999; 74: 1–6.
4. Rahmathullah L, *et al.* Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990; 323: 929–35.
5. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; 338: 67–71.
6. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; 304: 207–10.
7. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; 342: 7–12.
8. Herrera MG, *et al.* Vitamin A supplementation and child survival. *Lancet* 1992; 340: 267–71.
9. Gupta P, Indrayan A. Effect of vitamin A supplementation on childhood morbidity and mortality: critical review of Indian studies. *Indian Pediatr* 2002; 39: 1099–1118.

10. Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993; 306: 366–70.
11. Fawzi WW, *et al.* Vitamin A supplementation and child mortality: a meta-analysis. *JAMA* 1993; 269: 898–903.
12. Anonymous. Vitamin A and malnutrition/infection complex in developing countries. *Lancet* 1990; 336: 1349–51.
13. Humphrey JH, Rice AL. Vitamin A supplementation of young infants. *Lancet* 2000; 356: 422–4.
14. Villamor E, Fawzi WW. Vitamin A supplementation: implications for morbidity and mortality in children. *J Infect Dis* 2000; 182 (suppl): S122–S133.
15. Benn CS, *et al.* Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality. *BMJ* 2005; 331: 1428–32.
16. West KP, *et al.* Double blind, cluster randomised trial of low dose supplementation with vitamin A or β carotene on mortality related to pregnancy in Nepal. *BMJ* 1999; 318: 570–5. Correction. *ibid.*; 1386.
17. West KP, *et al.* Mortality of infants <6 mo of age supplemented with vitamin A: a randomized double-masked trial in Nepal. *Am J Clin Nutr* 1995; 62: 143–8.
18. Benn CS, *et al.* Effect of 50 000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial. *BMJ* 2008; 336: 1416–20.
19. Gogia S, Sachdev HS. Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. *BMJ* 2009; 338: b919.
20. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 1998; 352: 1257–63. Correction. *ibid.* 1999; 353: 154.
21. Rahmathullah L, *et al.* Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomised trial in southern India. *BMJ* 2003; 327: 254–7.
22. Humphrey JH, *et al.* Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *J Pediatr* 1996; 128: 489–96.
23. Semba RD, *et al.* Abnormal T-cell subset proportions in vitamin-A-deficient children. *Lancet* 1993; 341: 5–8.
24. Tleish JM. Vitamin A supplements in newborns and child survival. *BMJ* 2008; 336: 1385–6.
25. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 21/07/08).
26. Tyson JE, *et al.* Vitamin A supplementation for extremely-low-birth-weight infants. *N Engl J Med* 1999; 340: 1962–8.
27. Wardle SP, *et al.* Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2001; 84: F9–F13.
28. Shenai JP. Vitamin A supplementation in very low birth weight neonates: rationale and evidence. *Pediatrics* 1999; 104: 1369–74.
29. Mactier H, Weaver LT. Vitamin A and preterm infants: what we know, what we don't know, and what we need to know. *Arch Dis Child Fetal Neonatal Ed* 2005; 90: F103–F108.

ANAEMIA. A study among pregnant Indonesian women with nutritional anaemia (see Iron-Deficiency Anaemia, p. 2073.2) found a beneficial effect for vitamin A on haemoglobin when given with iron supplementation.[1] Similarly, in anaemic children given iron,[2] or adolescents given iron plus folic acid,[3] greater improvements in haemoglobin concentrations were seen with addition of vitamin A to supplementation. Vitamin A is considered essential for haematopoiesis; it has been suggested that vitamin A is required for the mobilisation and utilisation of iron for haemoglobin synthesis.[4] However, there are reports of anaemia caused by vitamin A supplementation, see Effects on the Blood, p. 2101.3.

1. Suharno D, *et al.* Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *Lancet* 1993; 342: 1325–8.
2. Mwanri L, *et al.* Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. *J Nutr* 2000; 130: 2691–6.
3. Ahmed F, *et al.* Concomitant supplemental vitamin A enhances the response to weekly supplemental iron and folic acid in anemic teenagers in urban Bangladesh. *Am J Clin Nutr* 2001; 74: 108–15.
4. van den Broek N. Anaemia and micronutrient deficiencies. *Br Med Bull* 2003; 67: 149–60.

DIARRHOEA. Although oral rehydration therapy remains the mainstay of the management of diarrhoea (p. 1805.2) once it develops, it has been suggested that vitamin A supplementation may be of use in reducing the incidence and mortality of diarrhoea during childhood. Several large mortality studies reported that vitamin A supplementation was associated with reduced mortality attributed to diarrhoea,[1-3] although another did not.[4] The effect on morbidity from diarrhoea is even less clear. A reduction in the severity, but not the incidence, of diarrhoea has been noted in two studies.[5,6] However, in one study in children with subclinical vitamin A deficiency, there was an increased prevalence of diarrhoea for 2 weeks after vitamin A supplementation,[7] and in another study, vitamin A increased the incidence of diarrhoea in children aged less than 30 months.[8] A meta-analysis[9] concluded that vitamin A supplementation has no consistent overall protective effect on the incidence of diarrhoea. While severity was not examined, they noted that the decrease in diarrhoea mortality rates but not incidence can be reconciled if vitamin A reduces diarrhoea severity and not susceptibility to infection. This is possibly supported by a study that found that a single high-dose vitamin A supplement, given with standard antibacterial treatment, reduced the severity of acute shigellosis in children in Bangladesh.[10] One group[11] proposed that the inconsistent findings on morbidity of vitamin A supplementation may be due to co-existing micronutrient deficiencies, such as zinc deficiency, that affect the bioavailability of vitamin A. They found combined zinc and vitamin A supplementation to be more effective in reducing persistent diarrhoea and dysentery than either zinc or vitamin A alone (see Vitamin A Deficiency, under Zinc, p. 2127.3).

1. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; 338: 67–71.
2. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; 304: 207–10.
3. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; 342: 7–12.
4. Vijayaraghavan K, *et al.* Effect of massive dose of vitamin A on morbidity and mortality in Indian children. *Lancet* 1990; 336: 1342–5.
5. Barreto ML, *et al.* Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* 1994; 344: 228–31.
6. Bhandari N, *et al.* Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. *BMJ* 1994; 309: 1404–7.
7. Stansfield SK, *et al.* Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 1993; 342: 578–82.
8. Dibley MJ, *et al.* Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 1996; 126: 434–42.
9. Grotto I, *et al.* Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. *J Pediatr* 2003; 142: 297–304.
10. Hossain S, *et al.* Single dose vitamin A treatment in acute shigellosis in Bangladeshi children: randomised double blind controlled trial. *BMJ* 1998; 316: 422–6.
11. Rahman MM, *et al.* Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001; 323: 314–18.

HIV INFECTION AND AIDS. A study in Malawi found that the rates of vertical transmission of HIV infection (birth of seropositive infants to seropositive mothers) were inversely related to maternal vitamin A status;[1] vitamin A deficiency during pregnancy was associated with a threefold to fourfold increased risk of mother-to-child transmission of HIV. This was not incompatible with the role of vitamin A in immunity and maintenance of mucosal surfaces, and since both HIV infection and pregnancy are risk factors for vitamin A deficiency, it was suggested that nutritional intervention to reduce vitamin A deficiency might help combat mother-to-child transmission. A South African study[2] found, in contrast, that supplementing HIV-infected pregnant women with vitamin A and betacarotene did not reduce the overall risk of vertical transmission to neonates. Supplementation did reduce the incidence of preterm births, and among these neonates, risk of perinatal HIV transmission was lower in those whose mothers had been supplemented. Vitamin A supplementation actually increased the risk of HIV transmission through breast feeding, with no effect on mortality at 24 months, in a Tanzanian trial.[3] Yet another study,[4] again in Tanzania, for which vertical transmission data were not available, found no evidence of an effect of vitamin A on birth outcomes in HIV-infected women and the authors pointed out that serum concentrations of vitamin A might be a marker of the stage of HIV disease rather than being causally related to outcome. The study did however find that multivitamin supplements reduced the risk of low birth-weight and size for age, and of premature birth, in the offspring of these women.[4] Interestingly, another trial in Tanzania found little difference between vitamin A supplementation and placebo on the progression of HIV disease and mortality. Multivitamin (excluding vitamin A) supplementation delayed disease progression and was associated with decreased mortality; addition of vitamin A to the multivitamin regimen reduced this benefit.[5] This is in contrast to 2 studies in Tanzania[6] and Uganda,[7] which found that vitamin A supplementation decreased mortality in children infected with HIV; however these results were not considered generalisable to communities with access to better healthcare and nutrition.

A systematic review and meta-analysis,[8] which included some of these conflicting studies, did not support the use of vitamin A supplementation to reduce the risk of vertical transmission and concluded that it may in fact increase the risk. Maternal vitamin A supplementation was not considered to decrease childhood mortality at 1 year. A further systematic review found no significant reduction in HIV progression in 6 studies of vitamin A or beta-carotene supplementation in adults. All-cause mortality was, however, halved in a meta-analysis of 3 studies in African children and short-term growth was improved in 1 study; the effect on diarrhoeal and respiratory morbidity was inconsistent.[9]

Means of reducing the risk of HIV infection in neonates are discussed under HIV Infection Prophylaxis, p. 959.1.

1. Semba RD, *et al.* Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet* 1994; 343: 1593–7.
2. Coutsoudis A, *et al.* Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. *AIDS* 1999; 13: 1517–24.
3. Fawzi WW, *et al.* Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. *AIDS* 2002; 16: 1935–44.
4. Fawzi WW, *et al.* Randomised trial of effects of vitamin supplements on pregnancy outcomes and T-cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998; 351: 1477–82.
5. Fawzi WW, *et al.* A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004; 351: 23–32.
6. Fawzi WW, *et al.* A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. *Pediatr Infect Dis J* 1999; 18: 127–33.
7. Semba RD, *et al.* Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus-infected children in Uganda: a controlled clinical trial. *Nutrition* 2005; 21: 25–31.
8. Mills EJ, *et al.* Vitamin supplementation for prevention of mother-to-child transmission of HIV and pre-term delivery: a systematic review of RCTs including more than 2800 women. *AIDS Res Ther* 2005; 2: 4.
9. Irlam JH, *et al.* Micronutrient supplementation in children and adults with HIV infection. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 22/12/10).

MEASLES. Vitamin A supplementation has an important role in the prevention of complications from measles.[1,2] Two studies specifically addressing vitamin A status and measles have found that complications such as pneumonia and diarrhoea were less common in children who had received supplements at the time of diagnosis than in those given a placebo.[3,4] WHO has recommended treating children in populations where vitamin A deficiency is common with high-dose vitamin A supplements during episodes of measles as follows:[5]

- all children over 12 months of age: 200 000 units
- those between 6 and 12 months of age: 100 000 units
- infants less than 6 months of age: 50 000 units

Doses are given on 2 consecutive days and followed by a third dose at least 2 weeks later.

Studies in the USA have indicated that even among well-nourished children from a developed country, vitamin A deficiency in measles patients is not uncommon,[6,7] and vitamin A supplementation needs to be considered in children at risk.[8]

1. Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993; 306: 366–70.
2. Fawzi WW, *et al.* Vitamin A supplementation and child mortality: a meta-analysis. *JAMA* 1993; 269: 898–903.
3. Barclay AJG, *et al.* Vitamin A supplements and mortality related to measles: a randomised clinical trial. *BMJ* 1987; 294: 294–6.
4. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990; 323: 160–4.
5. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia.* 2nd ed. Geneva: WHO,1997.
6. Arrieta AC, *et al.* Vitamin A levels in children with measles in Long Beach, California. *J Pediatr* 1992; 121: 75–8.
7. Butler JC, *et al.* Measles severity and serum retinol (vitamin A) concentration among children in the United States. *Pediatrics* 1993; 91: 1176–81.
8. Committee on Infectious Diseases of the American Academy of Pediatrics. Vitamin A treatment of measles. *Pediatrics* 1993; 91: 1014–15.

PREMATURITY. The fetus accumulates vitamin A in the third trimester, and most premature infants have low plasma vitamin A concentrations. Inadequate vitamin A supplementation after birth may exacerbate the problem, and contribute to an increased risk of developing chronic lung disease. A systematic review found that supplementing very low birth-weight infants with vitamin A was associated with a reduction in death or oxygen requirement at 1 month of age.[1]

1. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 12/03/08).

RESPIRATORY-TRACT INFECTIONS. Mortality studies did not show a consistent impact for vitamin A supplementation on death from non-measles-related respiratory infections.[1-3] Similarly, other studies have found no benefit of vitamin A on subsequent respiratory morbidity.[4-6] A meta-analysis of studies reporting pneumonia morbidity and mortality found no overall benefit or harm from vitamin A supplementation.[7] However, an increased prevalence of symptoms of respiratory infections associated with vitamin A supplementation has been noted in two studies,[8,9] particularly in children with adequate nutritional status. A meta-analysis of the effect of vitamin A supplementation on childhood morbidity found an increased incidence of respiratory-tract infections; since most trials had excluded children with overt vitamin A deficiency, the authors speculated that high-dose vitamin A given to children with adequate vitamin A stores might cause a temporary decline in immune status, increasing their susceptibility to infection.[10] A systematic review concluded that vitamin A should not be given to all children for *prevention* of acute lower respiratory-tract infections, but noted that children with vitamin A deficiency or poor nutritional status might benefit from supplementation in this respect.[11]

Vitamin A was not effective for the *treatment* of childhood non-measles-related lower respiratory-tract infections[12] or pneumonia.[13] Similarly, there was no benefit from vitamin A in the treatment of RSV infection in children in 2 studies.[14,15] In one of these studies there was a tendency for vitamin A to improve outcomes in the subgroup of severely ill children,[14] and in the other there was a slight increase in duration of hospitalisation in low-risk children receiving vitamin A.[15] A meta-analysis found no evidence that adjunctive treatment with high-dose vitamin A alters the course of pneumonia in children.[16]

1. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; 338: 67–71.
2. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; 304: 207–10.

3. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; 342: 7–12.
4. Barreto ML, *et al.* Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* 1994; 344: 228–31.
5. Bhandari N, *et al.* Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. *BMJ* 1994; 309: 1404–7.
6. Kartasasmita CB, *et al.* Plasma retinol level, vitamin A supplementation and acute respiratory infections in children of 1-5 years old in a developing country. *Tubercle Lung Dis* 1995; 76: 563–9.
7. The Vitamin A and Pneumonia Working Group. Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. *Bull WHO* 1995; 73: 609–19.
8. Stansfield SK, *et al.* Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 1993; 342: 578–82.
9. Dibley MJ, *et al.* Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 1996; 126: 434–42.
10. Grotto I, *et al.* Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. *J Pediatr* 2003; 142: 297–304.
11. Chen H, *et al.* Vitamin A for preventing acute lower respiratory tract infections in children up to seven years of age. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2008 (accessed 12/03/08).
12. Kjolhede CL, *et al.* Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. *J Pediatr* 1995; 126: 807–12.
13. Nacul LC, *et al.* Randomised, double blind, placebo controlled clinical trial of efficacy of vitamin A treatment in non-measles childhood pneumonia. *BMJ* 1997; 315: 505–10.
14. Dowell SF, *et al.* Treatment of respiratory syncytial virus infection with vitamin A: a randomised placebo-controlled trial in Santiago, Chile. *Pediatr Infect Dis J* 1996; 15: 782–6.
15. Bresee JS, *et al.* Vitamin A therapy for children with respiratory syncytial virus infection: a multicenter trial in the United States. *Pediatr Infect Dis J* 1996; 15: 777–82.
16. Brown N, Roberts C. Vitamin A for acute respiratory infection in developing countries: a meta-analysis. *Acta Paediatr* 2004; 93: 1437–42.

XEROPHTHALMIA. Vitamin A deficiency is responsible in many developing countries for visual problems that may culminate in xerophthalmia and blindness.[1] Supplementation with vitamin A as recommended by WHO and discussed under Deficiency states, p. 2099.2, will raise the vitamin A status of the individual and act prophylactically against the development of xerophthalmia. For the treatment of xerophthalmia (which includes night blindness, conjunctival xerosis with Bitot's spots, corneal xerosis, corneal ulceration, and keratomalacia) WHO have stated[2] that oral doses of vitamin A, preferably in an oil-based preparation, are the treatment of choice and should be given immediately the disorder is recognised in the following doses:

- patients over 1 year of age (with the exception of women of reproductive age): 200 000 units
- infants aged 6 to 12 months: 100 000 units
- those aged less than 6 months: 50 000 units

Doses should be repeated the next day, and again at least 2 weeks later.

In *women of reproductive age* there is a need to balance the possible teratogenic effects of vitamin A should they be pregnant (see Pregnancy, p. 2102.1) with the serious consequences of xerophthalmia. WHO recommend that when there are severe signs of active xerophthalmia (i.e. acute corneal lesions) high-dose vitamin A treatment should be given as described above for those aged over 1 year. When only less severe signs are present (night blindness, Bitot's spots), women of reproductive age should receive a daily oral dose of 5000 to 10 000 units for at least 4 weeks. Alternatively, a weekly dose of not more than 25 000 units may be substituted.

Although xerophthalmia is far less common in developed countries, vitamin A deficiency should be considered in all patients with recurrent conjunctival or corneal disorders associated with gastrointestinal or liver disease.[3]

1. Smith J, Steinemann TL. Vitamin A deficiency and the eye. *Int Ophthalmol Clin* 2000; 40: 83–91.
2. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia.* 2nd ed. Geneva: WHO,1997.
3. Watson NJ, *et al.* Vitamin A deficiency and xerophthalmia in the United Kingdom. *BMJ* 1995; 310: 1050–1. Correction. *ibid.*: 1320.

Malignant neoplasms. Epidemiological studies suggest that antoxidant vitamins such as the vitamin A substances may play a role in preventing the development of malignancy but there is currently little evidence from prospective studies that supplementation is helpful, and even some evidence of harm (see p. 2047.3). Conversely, synthetic retinoids such as tretinoin (all-*trans*-retinoic acid) have an established role in treating some cancers (see p. 1725.3).

Retinitis pigmentosa. Retinitis pigmentosa is the name applied to a group of slowly progressive hereditary degenerative diseases of the retina[1] that often result in blindness in adulthood. The rod and cone photoreceptors in the retina are primarily affected and initial symptoms include night blindness and intolerance to light. Later signs include infiltration of pigment from the retinal pigmentary epithelium into the retinal layers. Various treatments have been tried but none appear to have any proven benefit. Results of one large double-blind study[2] suggest that whereas treatment with vitamin A might slow the decline in visual acuity treatment with vitamin E appears to have a deleterious effect on the rate of decline. Vitamin E did appear to delay the rate of vision decline in 3 patients with retinitis pigmentosa and a defect in α-tocopherol-transfer protein associated with vitamin E deficiency.[3] Supplementation with 15 000 units of vitamin A daily for up to 12 years was considered to be safe in a study in adults with retinitis pigmentosa; no clinical manifestations of hepatotoxicity were apparent.[4] Addition of lutein to the vitamin A regimen has also been tried.[5] Docosahexaenoic acid has also been investigated, with variable results; some consider that vitamin A and oily fish in the diet could be beneficial in terms of visual preservation.[1] Transplantation of the retina is being investigated as a treatment for retinitis pigmentosa.[1,6] Devices to electrically stimulate the retina, optic nerve, or visual cortex are being developed.[1]

1. Hartong DT, *et al.* Retinitis pigmentosa. *Lancet* 2006; 368: 1795–1809.
2. Berson EL, *et al.* A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol* 1993; 111: 761–2.
3. Yokota T, *et al.* Retinitis pigmentosa and ataxia caused by a mutation in the gene for the α -tocopherol-transfer protein. *N Engl J Med* 1996; 335: 1770–1.
4. Sibulesky L, *et al.* Safety of <7500 RE (<25 000 IU) vitamin A daily in adults with retinitis pigmentosa. *Am J Clin Nutr* 1999; 69: 656–63.
5. Berson EL, *et al.* Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. *Arch Ophthalmol* 2010; 128: 403–11.
6. Anonymous. Transplantation as a therapy for retinitis pigmentosa? *Br J Ophthalmol* 1997; 81: 430.

Retinopathy of prematurity. There is some suggestion that vitamin A supplementation may reduce the incidence of retinopathy of prematurity (p. 2120.3).

Adverse Effects and Precautions

The use of excessive amounts of vitamin A substances over long periods can lead to toxicity. Rarely, acute toxicity may also occur with very high doses.

- *Hypervitaminosis A* (chronic toxicity) is characterised by fatigue, irritability, anorexia and loss of weight, vomiting and other gastrointestinal disturbances, low-grade fever, hepatomegaly, skin changes (yellowing, dryness, sensitivity to sunlight), pruritus, alopecia, dry hair, cracking and bleeding lips, anaemia, headache, hypercalcaemia, subcutaneous swelling, nocturia, and pains in bones and joints. Symptoms of chronic toxicity may also include raised intracranial pressure and papilloedema mimicking brain tumours, and visual disturbances which may be severe. Symptoms usually clear on withdrawal of vitamin A, but in children premature closure of the epiphyses of the long bones may result in arrested bone growth.
- *Acute vitamin A intoxication* is characterised by sedation, dizziness, confusion, diarrhoea and vomiting, sore mouth, bleeding gums, desquamation, and increased intracranial pressure (resulting in bulging fontanelle in infants or severe headache in adults). Hepatomegaly and visual disturbances may occur; irritability may be severe.

Hypervitaminosis A does not appear to be a problem with large doses of carotenoids (see Pharmacokinetics under Betacarotene, p. 2052.1).

Enhanced susceptibility to the effects of vitamin A may be seen in children and in patients with liver disease.

Excessive doses of vitamin A should be avoided in pregnancy because of potential teratogenic effects; for further details see Pregnancy, p. 2102.1.

Gastrointestinal absorption of vitamin A may be impaired in cholestatic jaundice and fat-malabsorption conditions.

Benign intracranial hypertension. High doses of vitamin A cause increased intracranial pressure, and, in infants, this is manifested as bulging of the fontanelle. In one study,[1] 11.5% of infants receiving 3 doses of 50 000 units of vitamin A at monthly intervals had bulging fontanelle, compared with 1% of infants receiving placebo. The bulging lasted between 24 and 72 hours and subsided without treatment,[1] and did not appear to be associated with any physical or developmental abnormalities on long-term follow-up.[2] In another study in neonates, bulging fontanelle occurred in 4.6% of recipients of vitamin A 50 000 units and 2.7% of placebo recipients 24 hours after the dose.[3] In contrast, less than 1% of infants given 3 doses of 25 000 units of vitamin A at monthly intervals had bulging fontanelle in a further study.[4]

1. de Francisco A, *et al.* Acute toxicity of vitamin A given with vaccines in infancy. *Lancet* 1993; 342: 526–7.
2. van Dillen J, *et al.* Long-term effect of vitamin A with vaccines. *Lancet* 1996; 347: 1705.
3. Agoestina T, *et al.* Safety of one 52 microMol (50 000 IU) oral dose of vitamin A administered to neonates. *Bull WHO* 1994; 72: 859–68.
4. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 1998; 352: 1257–63. Correction. *ibid.* 1999; 353: 154.

Carcinogenicity. For mention of the *increased* risk of lung cancer in high-risk individuals receiving betacarotene and vitamin A, when compared with placebo, in a study investigating vitamins in lung cancer prevention, see Prophylaxis of Malignant Neoplasms, p. 2047.3.

Effects on the blood. Normochromic macrocytic anaemia developed in a patient who had been receiving oral vitamin A 150 000 units daily for several months.[1] The patient's haemoglobin returned to normal when vitamin A was stopped, and the accompanying symptoms of perioral dermatitis and glossitis also disappeared. Similarly, normochromic normocytic anaemia and thrombocytopenia in an infant given 62 000 units daily for 80 days, resolved on stopping vitamin A.[2] In contrast, vitamin A has been reported to have a beneficial effect on anaemia, see under Deficiency states, p. 2100.1.

1. White JM. Vitamin-A-induced anaemia. *Lancet* 1984; ii: 573.
2. Perrotta S, *et al.* Infant hypervitaminosis A causes severe anemia and thrombocytopenia: evidence of a retinol-dependent bone marrow cell growth inhibition. *Blood* 2002; 99: 2017–22.

Effects on bone. Excessive dietary intake of vitamin A may be associated with osteoporosis. In an epidemiological study,[1] a dietary intake of retinol greater than 1500 micrograms daily (5000 units) doubled the risk of hip fracture compared with an intake of less than 500 micrograms daily (about 1670 units) in women (odds ratio, 2.1; 95% confidence interval 1.1 to 4.0). These data were confirmed by the Nurses' Health Study,[2] which found that postmenopausal women with the highest vitamin A and retinol intakes were at increased risk for hip fracture, irrespective of whether the intakes were from food plus supplements, or food alone. Women with daily retinol intakes of more than 1500 micrograms had a relative risk for hip fracture of 1.64 compared with those consuming less than 500 micrograms daily. Betacarotene intake, however, did not correlate significantly with an increased risk of fracture. A large cohort study[3] of men found that the overall risk of any fracture, including hip fractures, was substantially increased among men with the highest concentrations of serum retinol; there was no association between serum betacarotene levels and the risk of fracture. Subsequently, routine supplementation and the fortification of food with vitamin A in western countries has been questioned.[4] A report[5] from the UK Government's Scientific Advisory Committee on Nutrition cautions against the intake of more than 1.5 mg of vitamin A daily in those at increased risk of osteoporosis, such as postmenopausal women and the elderly. However, results from a cohort study in the elderly[6] suggest a U-shaped dose relationship, in that both high and low intakes of vitamin A were associated with reduced bone mineral density, and another study[7] in women aged between 50 and 74 years, found both high and low serum vitamin A concentrations to be associated with an increased risk of hip fracture. Another large observational epidemiological study from the Women's Health Initiative[8] did not show any association between vitamin A or retinol intake and the risk of fractures in postmenopausal women.

1. Melhus H, *et al.* Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann Intern Med* 1998; 129: 770–8.
2. Feskanich D, *et al.* Vitamin A intake and hip fractures among postmenopausal women. *JAMA* 2002; 287: 47–54.
3. Michaëlsson K, *et al.* Serum retinol levels and the risk of fracture. *N Engl J Med* 2003; 348: 287–94.
4. Lips P. Hypervitaminosis A and fractures. *N Engl J Med* 2003; 348: 347–9.
5. Scientific Advisory Committee on Nutrition. *Review of dietary advice on vitamin A.* London: The Stationery Office, 2005. Also available at: http://www.sacn.gov.uk/pdfs/sacn_vita_report.pdf (accessed 21/07/08)
6. Promislow JHE, *et al.* Retinol intake and bone mineral density in the elderly: the Rancho Bernardo Study. *J Bone Miner Res* 2002; 17: 1349–58.
7. Opotowsky AR, Bilezikian JP. Serum vitamin A concentration and the risk of hip fracture among women 50 to 74 years old in the United States: a prospective analysis of the NHANES I Follow-up Study. *Am J Med* 2004; 117: 169–74.
8. Caire-Juvera G, *et al.* Vitamin A and retinol intakes and the risk of fractures among participants of the Women's Health Initiative Observational Study. *Am J Clin Nutr* 2009; 89: 323–30.

Effects on the immune system. Vitamin A deficiency is generally associated with impaired immunity, and treatment of deficiency results in reductions in morbidity and mortality from a number of infectious diseases (see under Deficiency States, p. 2099.2). However, a few studies have shown increased prevalence of diarrhoea and/or respiratory-tract infections with high doses of vitamin A. There is a possibility that high single doses of vitamin A may temporarily attenuate the immune response in non-deficient children.[1] For the effect of high-dose vitamin A supplements on the response to measles vaccine in some studies, see p. 2399.3.

1. Anonymous. Childhood morbidity, immunity and micronutrients. *WHO Drug Inf* 1996; 10: 12–16.

Effects on the liver. Vitamin A is stored in the Dissë space of liver cells and excessive dosage can lead to fibrosis and obstruction of sinusoidal blood flow, causing non-cirrhotic

portal hypertension and hepatocellular dysfunction.[1] Although hepatotoxicity has typically been reported with habitual ingestion of doses of vitamin A greater than 50 000 units daily, a case of severe hepatic fibrosis, with jaundice and hepatomegaly, has been reported in a patient who had been taking 25 000 units daily for at least 6 years in a multivitamin supplement.[2]

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; ii: 440–4.
2. Kowalski TE, *et al.* Vitamin A hepatotoxicity: a cautionary note regarding 25,000 IU supplements. *Am J Med* 1994; 97: 523–8.

Effects on mortality. Vitamin A supplementation has been reported to have beneficial effects on childhood mortality, especially in developing countries, see Deficiency States, p. 2099.2 *et seq.* However, one systematic review[1] of neonatal vitamin A supplementation failed to find evidence of a reduction in mortality or morbidity, and another systematic review of antoxidant supplementation in adults concluded that vitamin A either singly or with other antoxidants increased mortality.[2]

1. Gogia S, Sachdev HS. Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. *BMJ* 2009; 338: b919.
2. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Hypersensitivity. Local inflammatory reactions and severe anaphylactoid reactions have occurred in patients receiving vitamin A injections, and are usually attributed to solubilisers such as polyoxyl castor oils (p. 2202.3), and, less commonly, polysorbates (p. 2204.1).

A case of cutaneous hypersensitivity to retinol palmitate itself has been described.[1]

1. Shelley WB, *et al.* Hypersensitivity to retinol palmitate injection. *BMJ* 1995; 311: 232.

Overdosage. Although no clinical manifestations of toxicity were seen in 3 boys who ingested large amounts of vitamin A, their serum retinol concentrations continued to rise over about 3 weeks, and took several months to normalise; the authors cautioned that the use of chewable vitamins resembling confectionery may increase the risk of overdose in children.[1]

1. Lam HS, *et al.* Risk of vitamin A toxicity from candy-like chewable vitamin supplements for children. *Pediatrics* 2006; 118: 820–4.

Pregnancy. The fact that synthetic vitamin A derivatives such as isotretinoin are teratogenic (p. 1709.3) has prompted concern about the potential teratogenicity of high doses of vitamin A.

A prospective cohort study found that a total daily intake of vitamin A from all sources of greater than 15 000 units during early pregnancy was associated with a significantly increased risk of birth defects of structures arising from the cranial neural crest.[1] When vitamin A intake from supplements was analysed separately, an apparent vitamin A threshold dose for the development of birth defects of 10 000 units daily was suggested. However, this study has been criticised[2,3] and some suggest the data allows for a higher threshold dose.[3] A further study found no significant difference in birth defect rates between women consuming greater than 8000 or 10 000 units of vitamin A daily in the period around conception (as supplements and fortified cereals) and those consuming less than 5000 units daily.[4]

After earlier case reports in the USA suggesting that large doses of vitamin A (equivalent to about ten times the daily recommended dietary allowance of 2250 units) taken in early pregnancy may cause birth defects, the UK Chief Medical Officer cautioned women against the use of vitamin A supplements except under medical supervision.[5] Additionally, advice was given that liver or liver products should not be eaten because high concentrations of vitamin A had been detected in some samples of animal liver. However, others thought that the avoidance of liver or liver products might result in inadequate nutrition in some and that a less alarmist view might have been to suggest a limitation on intake rather than total prohibition.[6,7] The Royal College of Obstetricians and Gynaecologists has advised that high-dose vitamin A supplementation (more than about 700 micrograms, or 2300 units daily) is not recommended during pregnancy.[8] The Australian Adverse Drug Reactions Advisory Committee has advised women in this category to avoid vitamin A supplements and not to exceed the recommended daily allowance of 2500 units from all sources.[9]

1. Rothman KJ, *et al.* Teratogenicity of high vitamin A intake. *N Engl J Med* 1995; 333: 1369–73.
2. Werler MM, *et al.* Teratogenicity of high vitamin A intake. *N Engl J Med* 1996; 334: 1195–6.
3. Watkins M, *et al.* Teratogenicity of high vitamin A intake. *N Engl J Med* 1996; 334: 1196.
4. Mills JL, *et al.* Vitamin A and birth defects. *Am J Obstet Gynecol* 1997; 177: 31–6.
5. DoH. *Women cautioned: watch your vitamin A intake.* London: Department of Health, 1990(18 October).
6. Nelson M. Vitamin A, liver consumption, and risk of birth defects. *BMJ* 1990; 301: 1176.
7. Senders TAB. Vitamin A and pregnancy. *Lancet* 1990; 336: 1375.
8. Royal College of Obstetricians and Gynaecologists. RCOG release: RCOG issues new guidance on vitamin supplementation in pregnancy (issued 19th October, 2009). Available at: http://www.rcog.org.uk/news/rcog-release-rcog-issues-new-guidance-vitamin-supplementation-pregnancy (accessed 15/02/10)
9. Adverse Drug Reactions Advisory Committee (ADRAC). Vitamin A and birth defects. *Aust Adverse Drug React Bull* 1996; 15: 14–15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9611.htm (accessed 21/07/08)

Interactions

Absorption of vitamin A from the gastrointestinal tract may be reduced by the presence of neomycin, colestyramine, or liquid paraffin.

There is an increased risk of hypervitaminosis A if vitamin A is given with synthetic retinoids such as acitretin, isotretinoin, and tretinoin.

There is conflicting evidence regarding the effect of vitamin A on the response to measles vaccine (see p. 2399.3).

Pharmacokinetics

Vitamin A substances are readily absorbed from the gastrointestinal tract but absorption may be reduced in the presence of fat malabsorption, low protein intake, or impaired liver or pancreatic function. Vitamin A esters are hydrolysed by pancreatic enzymes to retinol, which is then absorbed and re-esterified. Some retinol is stored in the liver. It is released from the liver bound to a specific α_1-globulin (retinol-binding protein) in the blood. The retinol not stored in the liver undergoes glucuronide conjugation and subsequent oxidation to retinal and retinoic acid; these and other metabolites are excreted in urine and faeces. Vitamin A does not readily diffuse across the placenta (but see Pregnancy, above), but is present in breast milk.

References.

1. Hartmann D, *et al.* Pharmacokinetic modelling of the plasma concentration-time profile of the vitamin retinyl palmitate following intramuscular administration. *Biopharm Drug Dispos* 1990; 11: 689–700.
2. Reinersdorff DV, *et al.* Plasma kinetics of vitamin A in humans after a single oral dose of [8,9,19-^{13}] retinyl palmitate. *J Lipid Res* 1996; 37: 1875–85.
3. Harrison EH, Hussain MM. Mechanisms involved in the intestinal digestion and absorption of dietary vitamin A. *J Nutr* 2001; 131: 1405–8.

Human Requirements

Dietary vitamin A is derived from 2 sources, *preformed retinoids* from animal sources such as liver, kidney, dairy produce, and eggs (fish-liver oils are the most concentrated natural source), and *provitamin carotenoids* which can be obtained from many plants; the latter are converted to retinol in the body but are less effectively utilised. Carotenes (α, β, and γ) are major sources and of these, β-carotene (betacarotene—see p. 2051.1) has the highest vitamin A activity and is the most plentiful in food. Variable amounts of β-carotenes are found in carrots and dark green or yellow vegetables. Red palm oil is a good source of α- and β-carotenes.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published[1] for vitamin A and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women (but see Pregnancy, above). In the UK the reference nutrient intake (RNI) for adult males and females is 700 and 600 micrograms retinol equivalents (about 2330 and 2000 units) daily, respectively and the estimated average requirement (EAR) is 500 and 400 micrograms retinol equivalents (about 1660 and 1330 units) daily, respectively. This UK report[1] also highlighted the toxicity associated with large doses of vitamin A and recommended that regular intakes should not exceed 9 mg (30 000 units) daily in adult men and 7500 micrograms (25 000 units) daily in adult women. (A later report[3] was unable to establish a safe upper level for vitamin A intake, but considered that total intakes above 1500 micrograms retinol equivalents daily might be inappropriate.) Figures were also given in the earlier report for infants and children who were said to be more sensitive to the effects of vitamin A. These limits did not apply to therapeutic doses of vitamin A used under medical supervision.[1] In pregnancy the RNI is 700 micrograms retinol equivalents (2330 units) daily and in nursing mothers 950 micrograms (3160 units) daily. In the USA the RDA for adults is 900 micrograms daily for men and 700 micrograms daily for women.[2] The tolerable upper intake level is 3 mg daily.

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 vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington DC: National Academy Press. 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 06/01/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: A-Vitel; Adermicina A Mama; Amenite A; Andrioderma; Arovit; Atomoderma A; Bagovit A; Cazmar; Cutidermin Crema Humect. con Vitamina A†; Domsedan; Flosen-A; Metabolite-A; Skinderm A; *Austral.*: Ungvita; *Belg.*: Vitamuruine; *Braz.*: Arovit; Lacrigel A; Retinar; *Canad.*: Arginax†; Arovit†; Theraplex AF; Vitapro A; *Chile*: Avitana†; Bagovit A; Microret†; *China*: Oculotect (诺神); *Cz.*: Axerophthol; *Denm.*: A-vitamin; *Fr.*: A 313; A 313; Avibon; *Ger.*: Augenschutz NA; Oculotect†; Solan-M†; Vitafluid; Vitagel; *Gr.*: Avitan; *Hung.*: Oculotect; *India*: Arovit; Lipolotion; Mixcarotin; *Israel*: Avipur†; *Ital.*: Arovit; Euvitol; Vit-A-N; *Malaysia*: Fairy ADE; *Mex.*: A Grin†; Acon; Dermotin A; Microret; Microvita†; Palmyforte; Retigel-A; *NZ*: Dermalife†; Ungvita; *Philipp.*: Afaxin; Alici-A; Hypotears; Retimax; *Pol.*: Aksoderm; Dermosavit; Dermovit A; Masc Ochronna z Witamina A; Masc Witaminowa Ochronna; *Port.*: A-Vite; Vitaminoftalmina; *Rus.*: Videstim (Видестим); Vita-POS (Вита-ПОС); *S.Afr.*: Arovit†; *Spain*: Auxina A Masiva; Biominol; Rinocusi Vitaminico; Rinovitex; *Swed.*: Arovit†; *Switz.*: Oculotect; Vita-POS; *Thai.*: Cebrin-Fe; *Turk.*: Avicap; Avigen; Carovigen; *UK*: Biovit-A; *USA*: Aquasol A; Palmitate-A†; Pedi-Vit-A; Retinol-A; *Venez.*: Alfa-Mon; Retiva.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Paediatric Vitamins A, C and D Oral Drops;
BPC 1973: Vitamins A and D Capsules;
USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; 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 Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Oleovitamin A and D Capsules; Oleovitamin A and D; Vitamin A Capsules; Vitamin A Oral Liquid Preparation; Vitamin A Tablets.

Vitamin B Substances

Vitamina B, grupo de la; Витамины Группы В.

The B vitamin group includes the B_1 substances (thiamine and its derivatives), B_2 (riboflavin), B_6 (pyridoxine and derivatives), and B_{12}(the cobalamins). In addition, nicotinic acid and its derivatives (p. 2083.1) and folic acid (p. 2063.1) are held to be part of the group, as is pantothenic acid (p. 2085.2), but these latter substances are not generally referred to by their traditional B nomenclature.

Vitamin B_1 Substances

Vitamina B_1; Витамины Группы B_1.

Acetiamine Hydrochloride *(rINNM)*

Acethiamine Hydrochloride; Acetiamina, hidrocloruro de; Acétiamine, Chlorhydrate d'; Acetiamini Hydrochloridum; Diacethiamine Hydrochloride; Hidrocloruro de acetiamina; Ацетиамина Гидрохлорид.

N-(5-Acetoxy-3-acetylthiopent-2-en-2-yl)-*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide hydrochloride monohydrate.

$C_{19}H_{22}N_4O_4S.HCl.H_2O$=420.9

CAS — 299-89-8 (acetiamine).

UNII — W024X5P395.

Benfotiamine *(rINN)*

Benfotiamina; Benfotiaminum; *S*-Benzoylthiamine *O*-Monophosphate; Monofosfato de benzoiltiamina; Бенфотиамин.

N-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-(2-benzoylthio-4-dihydroxyphosphinyloxy-1-methylbut-1-enyl)formamide.

$C_{19}H_{23}N_4O_6PS$=466.4

CAS — 22457-89-2.

ATC — A11DA03.

ATC Vet — QA11DA03.

UNII — Y92OUS2H98.

Bisbentiamine *(rINN)*

O-Benzoylthiamine Disulphide; Bisbentiamina; Bisbentiaminum; Бисбентиамин.
NN'-[Dithiobis[2-(2-benzoyloxyethyl)-1-methylvinylene]]bis[*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide].
$C_{38}H_{42}N_8O_6S_2$=770.9
CAS — 2667-89-2.
UNII — MEI78CAM16.

Cocarboxylase *(BAN, rINN)*

Cocarboxilasa; Co-carboxylase; Cocarboxylasum; Diphosphothiamine; Pyruvodehydrase; Thiamine Pyrophosphate; Кокарбоксилаза.
3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-[2-[dihydroxyphosphinyloxy(hydroxy)phosphinyloxy]ethyl]-4-methylthiazolium hydroxide.
$C_{12}H_{20}N_4O_8P_2S$ (hydroxide form)=442.3
CAS — 154-87-0 (cocarboxylase chloride).
UNII — Q57971654Y.

Pharmacopoeias. *Pol.* includes the chloride.

Cycotiamine *(rINN)*

CCT; Cicotiamina; Cyclocarbothiamine; Cycotiaminum; Цикотиамин.
N-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-[1-(2-oxo-1,3-oxathian-4-ylidene)ethyl]formamide.
$C_{13}H_{16}N_4O_3S$=308.4
CAS — 6092-18-8.
UNII — FT8753F8R9.

Fursultiamine *(rINN)*

Fursultiamina; Fursultiaminum; Thiamine Tetrahydrofurfuryl Disulphide; TTFD; Фурсультиамин.
N-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-[4-hydroxy-1-methyl-2-(tetrahydrofurfuryldithio)but-1-enyl]formamide.
$C_{17}H_{26}N_4O_3S_2$=398.5
CAS — 804-30-8.
UNII — 05J6126SPX.

Octotiamine *(rINN)*

Octotiamina; Octotiaminum; Oktotiamiini; Oktotiamin; TATD; Thioctothiamine; Октотиамин.
N-[2-(3-Acetylthio-7-methoxycarbonylheptyldithio)-4-hydroxy-1-methylbut-1-enyl]-*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide.
$C_{23}H_{36}N_4O_5S_2$=544.7
CAS — 137-86-0.
UNII — UN1Q7096GA.

Prosultiamine *(rINN)*

DTPT; Prosultiamina; Prosultiaminum; Thiamine Propyl Disulphide; Просультиамин.
N-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-(4-hydroxy-1-methyl-2-propyldithiobut-1-enyl)formamide.
$C_{15}H_{24}N_4O_2S_2$=356.5
CAS — 59-58-5.
UNII — UI32MM3XE3.

Sulbutiamine *(rINN)*

Bisibutamina; Bisibutiamine; *O*-Isobutyrylthiamine Disulphide; Sulbutiamina; Sulbutiaminum; Сульбутиамин.
NN'-[Dithiobis[2-(2-isobutyryloxyethyl)-1-methylvinylene]] bis[*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide].
$C_{32}H_{46}N_8O_6S_2$=702.9
CAS — 3286-46-2.
ATC — A11DA02.
ATC Vet — QA11DA02.
UNII — 42NCM1BW43.

Thiamine Hydrochloride *(BANM, rINNM)*

Aneurine Hydrochloride; Cloruro de tiamina; Hidrocloruro de aneurina; Hidrocloruro de tiamina; Thiamin Hydrochloride; Thiaminchloridhydrochlorid; Thiamine, chlorhydrate de; Thiamine Chloride; Thiamin-hydrochlorid; Thiamini Hydrochloridum; Thiamini Chloridum; Tiamiinihydroklotidi; Tiamina, hidrocloruro de; Tiamin-hidroklorid; Tiaminhydroklorid; Tiamino hidrochloridas; Tiaminy chlorowodorek; Vitamin B_1; Vitamina B1; Тиамина Гидрохлорид.
3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochloride.
$C_{12}H_{17}ClN_4OS.HCl$=337.3
CAS — 59-43-8 (thiamine); 67-03-8 (thiamine hydrochloride).
ATC — A11DA01.
ATC Vet — QA11DA01.
UNII — M572600E5P.

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

Thiamine hydrobromide is included in *Int.*

Ph. Eur. 8: (Thiamine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol; soluble in glycerol. A 2.5% solution in water has a pH of 2.7 to 3.3. Store in nonmetallic containers. Protect from light.

USP 36: (Thiamine Hydrochloride). White crystals or crystalline powder, usually having a slight, characteristic odour. When exposed to air, the anhydrous product rapidly absorbs about 4% of water. Soluble 1 in 1 of water and 1 in 170 of alcohol; insoluble in ether and in benzene; soluble in glycerol. pH of a 1% solution in water is between 2.7 and 3.4. Store in airtight containers. Protect from light.

Stability. Sterile thiamine hydrochloride solutions of pH 4 or less lose activity only very slowly but neutral or alkaline solutions deteriorate rapidly, especially in contact with air.

Thiamine Nitrate *(BANM, rINNM)*

Aneurine Mononitrate; Mononitrato de tiamina; Nitrato de tiamina; Thiamine Mononitrate; Thiamine, Nitrate de; Thiamini Nitras; Thiaminnitrat; Thiamin-nitrát; Tiamiininitraatti; Tiamina, nitrato de; Tiaminnitrat; Tiamin-nitrat; Tiamino nitratas; Tiaminy azotan; Vitamin B_1 Mononitrate; Тиамина Нитрат.
3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium nitrate.
$C_{12}H_{17}N_5O_4S$=327.4
CAS — 532-43-4.
ATC — A11DA01.
ATC Vet — QA11DA01.
UNII — 8K0I04919X.

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

Ph. Eur. 8: (Thiamine Nitrate). A white or almost white, crystalline powder or small, colourless crystals. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in alcohol and in methyl alcohol. A 2% solution in water has a pH of 6.8 to 7.6. Store in nonmetallic containers. Protect from light.

USP 36: (Thiamine Mononitrate). White crystals or crystalline powder, usually having a slight characteristic odour. Soluble 1 in 44 of water; slightly soluble in alcohol; very slightly soluble in chloroform. pH of a 2% solution in water is between 6.0 and 7.5. Store in airtight containers. Protect from light.

Uses and Administration

Thiamine is a water-soluble vitamin, although some of its derivatives have greater lipophilicity. It is an essential coenzyme for carbohydrate metabolism in the form of the diphosphate (thiamine pyrophosphate, cocarboxylase). Thiamine deficiency develops when the dietary intake is inadequate; severe deficiency leads to the development of a syndrome known as beri-beri. Chronic 'dry' beri-beri is characterised by peripheral neuropathy, muscle wasting and muscle weakness, and paralysis. Acute 'wet' beri-beri is characterised by cardiac failure and oedema. Wernicke-Korsakoff syndrome (demyelination of the CNS) may develop in severe cases of thiamine deficiency notably in association with chronic alcoholism. Severe thiamine deficiency, characterised by lactic acidosis and neurological deterioration, has been reported within a relatively short time of starting thiamine-free total parenteral nutrition; some deaths have occurred.

Thiamine is used in the treatment and prevention of thiamine deficiency. It is given orally, the preferred route, or if necessary by the intramuscular or intravenous routes (but see Hypersensitivity, p. 2104.1); intravenous injections should be given slowly over 30 minutes. In the treatment of mild chronic thiamine deficiency usual oral doses of 10 to 50 mg daily, in single or divided doses, have been recommended. In severe thiamine deficiency doses of up to 300 mg daily are given, and even higher daily doses may be used in Wernicke-Korsakoff syndrome by the intravenous route. For use in children see below.

Thiamine is usually given as either the hydrochloride or nitrate salts although other salts such as the dicamsylate, disulfide, monophosphate (monophosphothiamine) or pyrophosphate (cocarboxylase) may be used.

Other compounds that possess vitamin B_1 activity and may be given as alternatives to thiamine include benfotiamine, cycotiamine, octotiamine, prosultiamine, and sulbutiamine. Acetiamine, bisbentiamine, and fursultiamine have also been used.

Administration in children. Thiamine is licensed in the UK for oral use in children from 3 years of age in the treatment of **deficiency**; doses are similar to those in adults, above. However, management of vitamin B deficiency in children is usually with compound preparations also containing riboflavin and nicotinamide. The *BNFC* recommends the following oral doses of thiamine hydrochloride by age, as part of such a compound preparation:

- 1 month to 1 year: 5 mg three times daily (treatment) or once daily (prophylaxis)
- 1 to 12 years: 10 mg three times daily (treatment), or 5 mg twice daily (prophylaxis)
- 12 to 18 years: 10 to 15 mg three times daily (treatment) or 5 mg three times daily (prophylaxis)

Thiamine may also be used in the management of certain mitochondrial disorders. The *BNFC* recommends an oral dose of 5 mg/kg daily, adjusted as necessary, in neonates and children up to 18 years of age with **maple syrup urine disease.**

In the treatment of other metabolic disorders including **congenital lactic acidosis** thiamine may be given orally or by intravenous infusion over 30 minutes in the following doses:

- up to 1 month: 50 to 200 mg daily, as a single daily dose or in 2 to 3 divided doses, adjusted as necessary
- 1 month to 18 years: 100 to 300 mg daily, as a single dose or in 2 to 3 divided doses, adjusted as necessary. Up to 2 g daily may be necessary

Diabetes mellitus. Low plasma thiamine concentrations have been found[1] in patients with type 1 and type 2 diabetes mellitus In a small placebo-controlled study, benfotiamine 100 mg given orally four times daily significantly improved neuropathic pain in patients with diabetic polyneuropathy (see p. 8.2).[2]

1. Thomalley PJ, *et al.* High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. *Diabetologia* 2007; **50**: 2164–70.
2. Haupt E, *et al.* Benfotiamine in the treatment of diabetic polyneuropathy—a three-week randomized, controlled pilot study (BEDIP Study). *Int J Clin Pharmacol Ther* 2005; **43**: 71–7.

Wernicke-Korsakoff syndrome. The Wernicke-Korsakoff syndrome is a manifestation of thiamine deficiency seen particularly in alcoholics, but which may accompany other conditions including starvation or prolonged fasting, or persistent vomiting. It was originally classified as two separate disorders, Wernicke's encephalopathy and Korsakoff's syndrome, but these are now thought to represent aspects of a single pathological process.[1,2]

Classical Wernicke's symptoms comprise confusion, ataxia, ophthalmoplegia, and nystagmus. Ophthalmoplegia and ataxia may precede the mental symptoms by some days. Hypothermia may be seen, and collapse and sudden death may occur in some patients. The manifestations of Korsakoff's syndrome are short-term memory loss, learning deficits, and confabulation. The conditions are associated with demyelination and glial proliferation, as well as haemorrhagic lesions, mainly in the periventricular regions of the brain; characteristic biochemical abnormalities include raised serum-pyruvate concentration, which has been postulated as a cause of encephalopathy.[3]

Early recognition and treatment is important, both because of the risk of collapse and sudden death,[4] and to prevent irreversible damage to the CNS.[5] Korsakoff symptoms respond less well to treatment than those associated with Wernicke's encephalopathy,[6] and may indeed only become evident on treatment.

Treatment is with parenteral thiamine, preferably intravenously, to ensure adequate absorption; any risks of parenteral treatment are considered justifiable.[1,2,5,7,8] Low dose parenteral therapy (100 to 250 mg daily) may not restore vitamin status or improve symptoms, and it is generally agreed that higher doses are required.[1,7] Although the optimal treatment regimen for thiamine is not established,[9] typical doses range from 500 to 750 mg given intravenously with other vitamins three times daily for at least 2 days;[5] Up to 1 g thiamine per dose has been used.[8] If there is a response, some recommend continued treatment with 250 mg intravenously or intramuscularly once daily for 5 days or until there is no further improvement.[5,8] Response varies according to the presenting condition, with ocular symptoms responding more rapidly than confusion; however, a noticeable improvement in delirium and acute confusion is said to occur within 1 or 2 days in most cases.[1] Cognitive impairment responds more slowly, if at all.[9] Prophylactic thiamine is considered appropriate in patients at high risk of deficiency such as those undergoing alcohol withdrawal and with signs of malnutrition; an intramuscular or intravenous dose of 250 mg once daily for 3 to 5 days has been used.[1,5,8] In lower risk patients with mild deficiency, an oral dose of thiamine 200 mg daily, given with other B vitamins, is often used.[5] Even several months after the onset of symptoms, treatment with high doses of thiamine has occasionally resulted in recovery.[10] The effects of the syndrome on memory are much harder to reverse.

Some 25% of patients make a full, and 50% a partial, recovery.[6]

1. Cook CCH, *et al.* B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. *Alcohol Alcohol* 1998; 33: 317–36.
2. Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol* 2000; 35 (suppl): 2–7.
3. Petrie WM, Ban TA. Vitamins in psychiatry: do they have a role? *Drugs* 1985; 30: 58–65.
4. Reuler JB, *et al.* Wernicke's encephalopathy. *N Engl J Med* 1985; 312: 1035–9.
5. Thomson AD, *et al.* Royal College of Physicians, London. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and emergency department. *Alcohol Alcohol* 2002; 37: 513–21. Correction. *ibid.* 2003; 38: 291.
6. Anonymous. Korsakoff's syndrome. *Lancet* 1990; 334: 912–13.
7. Cook CCH, Thomson AD. B-complex vitamins in the prophylaxis and treatment of Wernicke-Korsakoff syndrome. *Br J Hosp Med* 1997; 57: 461–5.
8. Cook CCH. Prevention and treatment of Wernicke-Korsakoff syndrome. *Alcohol Alcohol* 2000; 35 (suppl): 19–20.
9. Day E, *et al.* Thiamine for Wernicke-Korsakoff syndrome in people at risk from alcohol abuse. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2004 (accessed 16/02/10).
10. Caroza A, Schnider A. Dramatic recovery from prolonged Wernicke-Korsakoff disease. *Eur Neurol* 2005; 53: 45–6.

Adverse Effects and Precautions

Adverse effects with thiamine are rare, but hypersensitivity reactions have occurred, mainly after parenteral doses. These reactions have ranged in severity from very mild to, very rarely, fatal anaphylactic shock (see below).

Breast feeding. Supplementation did not significantly affect thiamine concentration in breast milk of healthy, well-nourished women when compared with those not given thiamine; the authors supposed that absorptive capacity of the mammary gland may be saturable.[1] Based on this, the American Academy of Pediatrics considers its use to be usually compatible with breast feeding.[2]

1. Nail PA, *et al.* The effect of thiamin and riboflavin supplementation on the level of those vitamins in human breast milk and urine. *Am J Clin Nutr* 1980; 33: 198–204.
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 09/01/06)

Hypersensitivity. The UK CSM had received, between 1970 and July 1988, 90 reports of adverse reactions associated with the use of an injection containing high doses of vitamins B and C. The most frequent reactions were anaphylaxis (41 cases, including 2 fatalities), dyspnoea or bronchospasm (13 cases), and rash or flushing (22 cases); 78 of the reactions occurred during, or shortly after, intravenous injection and the other 12 after intramuscular injection.[1] They recommended that parenteral treatment be used only when essential, and that, when given, facilities for treating anaphylaxis should be available. They also recommended that, when the intravenous route was used, the injection be given slowly (over 10 minutes). Various authors[2,3] have noted that parenteral treatment is *essential* for the prophylaxis and treatment of Wernicke's encephalopathy (see p. 2103.3). However, further reports of anaphylaxis to parenteral thiamine have since been described,[4–6] including one with a fatal outcome.[4]

1. CSM. Parentrovite & allergic reactions. *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 17/04/09)
2. Wrenn KD, Slovis CM. Is intravenous thiamine safe? *Am J Emerg Med* 1992; 10: 165.
3. Thomson AD, Cook CCH. Parenteral thiamine and Wernicke's encephalopathy: the balance of risks and concerns. *Alcohol Alcohol* 1997; 32: 207–9.
4. Van Haecke P, *et al.* Thiamine-induced anaphylactic shock. *Am J Emerg Med* 1995; 13: 371–2.
5. Morinville V, *et al.* Anaphylaxis to parenteral thiamine (vitamin B1). *Schweiz Med Wochenschr* 1998; 128: 1743–4.
6. Johri S, *et al.* Anaphylaxis from intravenous thiamine—long forgotten? *Am J Emerg Med* 2000; 18: 642–3.

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Small amounts of thiamine are well absorbed from the gastrointestinal tract after oral doses, but the absorption of doses larger than about 5 mg is limited. It is also rapidly absorbed on intramuscular injection. It is widely distributed to most body tissues, and appears in breast milk. Within the cell, thiamine is mostly present as the diphosphate. Thiamine is not stored to any appreciable extent in the body and amounts in excess of the body's requirements are excreted in the urine unchanged or as metabolites.

References.
1. Weber W, *et al.* Nonlinear kinetics of the thiamine cation in humans: saturation of nonrenal clearance and tubular reabsorption. *J Pharmacokinet Biopharm* 1990; 18: 501–23.
2. Tallaksen CME, *et al.* Kinetics of thiamin and thiamin phosphate esters in human blood, plasma and urine after 50 mg intravenously or orally. *Eur J Clin Pharmacol* 1993; 44: 73–8.
3. Loew D. Pharmacokinetics of thiamine derivatives especially of benfotiamine. *Int J Clin Pharmacol Ther* 1996; 34: 47–50.
4. Greb A, Bitsch R. Comparative bioavailability of various thiamine derivatives after oral administration. *Int J Clin Pharmacol Ther* 1998; 36: 216–21.
5. Frank T, *et al.* High thiamine diphosphate concentrations in erythrocytes can be achieved in dialysis patients by oral administration of benfotiamine. *Eur J Clin Pharmacol* 2000; 56: 251–7.
6. Drewe J, *et al.* Effect of intravenous infusions of thiamine on the disposition kinetics of thiamine and its pyrophosphate. *J Clin Pharm Ther* 2003; 28: 47–51.

Human Requirements

Thiamine requirements are directly related to the carbohydrate intake and the metabolic rate. A daily dietary intake of about 0.9 to 1.5 mg of thiamine is recommended for healthy men and about 0.8 to 1.1 mg for healthy women. Cereals, nuts, peas, beans, yeast, and pork are rich sources of thiamine. Some other meats especially liver or kidneys, and also fish, contain significant amounts. Flour and bakery products are often enriched with thiamine. Considerable losses of thiamine may result from cooking processes.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published for thiamine[1] and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] In the UK for adult males and females the reference nutrient intake (RNI) is 400 micrograms per 1000 kcal daily and the estimated average requirement (EAR) is 300 micrograms per 1000 kcal daily. In the USA an RDA of 1.2 mg daily in adult males and 1.1 mg daily in females is recommended.

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 thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Megastene; Tiavit; *Austral.*: Betamin; *Austria*: Beneuran†; Bevitol; *Belg.*: Benerva; Betamine; *Braz.*: Acesyl; Arcalion; Benerva; Beneum; Beum; Ponti; Nervamin; Nerven; Neurivit; Vitaum; *Canad.*: Betaxin; Thiamiject; *Chile*: Arcalion; *China*: Bai Pu Li (百扶力); Qi Cun (齐存); Xin Yuan Da (欣源达); *Cz.*: Benfogamma; Thiabene; *Denm.*: BIOrto B1; *Fin.*: Neuramin; *Fr.*: Arcalion; Benerva; Bevitine; *Ger.*: B1-ASmedic; Betabion†; Milgamma mono; Milgamma protekt; Novirell B_1; *Gr.*: Arcalion; Benerva; *Hong Kong*: Aneubion†; Arcalion; Bevit†; Neo-Active Vit B-1†; Super B1; *Hung.*: Benfogamma; Beres B1; *India*: Arcalion; Benalgis; Benfage; Berin; *Indon.*: Alinamin; Arcalion; Beston; Licobevit; *Ital.*: Benerva; Dobetin Vitamina B1; *Jpn*: Alinamin-F; Neuvita; *Malaysia*: Arcalion; *Mex.*: Arcalion; Benal; Benerva; Carzilasa; Fortical; MTX-2 Alf; X-2; *Philipp.*: Arcalion; Drexabion; Hybutin; Jaga; Lixtress; Meganerv; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Supraneuron; Vineuron; *Pol.*: Benfogamma; *Port.*: Arcalion; Trifosfaneurina; Vitanidia†; *Rus.*: Benfogamma (Бенфогамма); Enerion (Энерион); Vitagamma (Витагамма); *Singapore*: Arcalion; *Spain*: Arcalion; Benerva; Surmenalit; *Swed.*: Benerva†; Betabion†; *Switz.*: Arcalion; Benerva; *Thai.*: Alinamin-F; Arcalion†; Beratex; Besasin; Chlorbicap; Menamin; Vitabee-1-10; *Turk.*: Arcalion; Bevigen; *UAE*: Thiavit; *UK*: Benerva; Tyvera; *Ukr.*: Benfogamma (Бенфогамма); Enerion (Энерион); *Venez.*: Arcalion; Beplus.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in. *Indon.*: Nufadoxin.

Homoeopathic Preparations. *Ger.*: Infl-Symphytum.

Pharmacopoeial Preparations

BP 2014: Thiamine Injection; Thiamine Tablets; Vitamins B and C Injection;

BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;

USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; 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; Thiamine Hydrochloride Elixir; Thiamine Hydrochloride Injection; Thiamine Hydrochloride Tablets; Thiamine Mononitrate Elixir; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Vitamin B_2 Substances

Vitamina B_2; Витамины Группы B_2

Riboflavin *(BAN, rINN)*

E101; Lactoflavin; Lactoflavina; Riboflaviini; Riboflavina; Riboflavinas; Riboflavine; Riboflavinum; Ryboflawina; Vitamin B_2; Vitamina G; Vitamina B_2; Рибофлавин; 7,8-Dimethyl-10-(1′-D-ribityl)isoalloxazine; 3,10-Dihydro-7,8-dimethyl-10-(D-*ribo*-2,3,4,5-tetrahydroxypentyl)benzopteridine-2,4-dione.

$C_{17}H_{20}N_4O_6$=376.4

CAS — 83-88-5.

ATC — A11HA04.

ATC Vet — QA11HA04.

UNII — TLM2976OFR.

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

Ph. Eur. 8: (Riboflavin). A yellow or orange-yellow crystalline powder. It exhibits polymorphism. Very slightly soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light. Solutions deteriorate on exposure to light, especially in the presence of alkali.

USP 36: (Riboflavin). A yellow to orange-yellow crystalline powder, having a slight odour. When dry, it is not appreciably affected by diffused light, but in solution light induces quite rapid deterioration, especially in the presence of alkalis. Very slightly soluble in water, in alcohol, and in isotonic sodium chloride solution; insoluble in chloroform and in ether; soluble in dilute solutions of alkalis. Its saturated solution in water is neutral to litmus. Store in airtight containers. Protect from light.

Riboflavin Sodium Phosphate *(BANM, rINNM)*

Fosfato sódico de riboflavina; Natrii Riboflavini Phosphas; Riboflaviininatriumfosfaatti; Riboflavin fosfát sodná sůl; Riboflavin 5′-Phosphate Sodium; Riboflavina, fosfato sódico de; Riboflavine, Phosphate Sodique de; Riboflavine Phosphate (Sodium Salt); Riboflavine Sodium Phosphate; *Riboflavin-foszfát-nátrium*; Riboflavini natrii phosphas; Riboflavinnatriumfosfat; Riboflavino natrio fosfatas; Riboflavin-phosphat-Natrium; Vitamin B_2 Phosphate; Натрия Рибофлавина Фосфат.

The sodium salt of riboflavin 5′-phosphate.

$C_{17}H_{20}N_4NaO_9P$=478.3

CAS — 130-40-5.

UNII — 20RD1DZH99.

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

Chin. and *US* specify the dihydrate salt.

Ph. Eur. 8: (Riboflavin Sodium Phosphate). A yellow or orange-yellow, hygroscopic, crystalline powder. Soluble in water; very slightly soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Riboflavin 5′-Phosphate Sodium). A fine, orange-yellow, hygroscopic, crystalline powder, having a slight odour. When dry, it is not affected by diffused light, but when in solution light induces rapid deterioration. Sparingly soluble in water. pH of a 1% solution in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Uses and Administration

Riboflavin, a water-soluble vitamin, is essential for the utilisation of energy from food. The active, phosphorylated forms, flavine mononucleotide (FMN) and flavine adenine dinucleotide (FAD), are involved as coenzymes in oxidative/reductive metabolic reactions. Riboflavin is also necessary for the functioning of pyridoxine and nicotinic acid.

Riboflavin deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a well-defined syndrome known as ariboflavinosis, characterised by cheilosis, angular stomatitis, glossitis, keratitis, surface lesions of the genitalia, and seborrhoeic dermatitis. There may also be normocytic anaemia and ocular symptoms including itching and burning of the eyes, and corneal vascularisation. Some of these symptoms may, in fact, be due to other vitamins such as pyridoxine or nicotinic acid which do not function correctly in the absence of riboflavin. Riboflavin deficiency may also occur with other vitamin B-complex deficiency states such as pellagra.

Riboflavin is used in the treatment and prevention of riboflavin deficiency. It is usually given in oral doses of 1 or 2 mg for prophylaxis; up to 30 mg daily in divided doses is used for treatment. For administration in children see p. 2105.1. Riboflavin, as the sodium phosphate, is also a component of intramuscular or intravenous vitamins B and

C injections; riboflavin sodium phosphate 1.27 g is equivalent to about 1 g of riboflavin.

Riboflavin tetrabutyrate has also been used.

Riboflavin is also used as a colouring agent for food.

Administration in children. In the UK, management of **vitamin B deficiency** in children is usually with compound preparations also containing thiamine and nicotinamide. The *BNFC* recommends the following oral doses of riboflavin by age, as part of such a compound preparation:

- 1 month to 1 year: 2 mg three times daily (treatment) or once daily (prophylaxis)
- 1 to 12 years: 4 mg three times daily (treatment), or 2 mg twice daily (prophylaxis)
- 12 to 18 years: 4 to 6 mg three times daily (treatment) or 2 mg three times daily (prophylaxis)

Riboflavin may also be used in the management of certain **metabolic disorders**. The *BNFC* recommends the following oral doses:

- up to 1 month: 50 mg once or twice daily, adjusted according to response
- 1 month to 18 years: 50 to 100 mg once or twice daily, adjusted according to response; up to 400 mg daily has been given

See also Glutaric Aciduria, below.

Glutaric aciduria. Milder forms of glutaric aciduria type II (p. 1559.2) may respond to riboflavin.[1] Treatment with riboflavin 50 mg daily resulted in progressive improvement in a 4-year-old boy, with full recovery after 1 year. His brother, who had sustained permanent brain damage after epileptic seizures, showed moderate clinical improvement with riboflavin therapy.[2] In an adult patient with a history of recurrent pancreatitis and exercise intolerance, treatment with riboflavin 120 mg daily and levocarnitine resulted in no further episodes, although abnormal concentrations of amino acids were still apparent in her urine.[3]

1. Gregersen N, *et al.* Riboflavin responsive glutaric aciduria type II. *Prog Clin Biol Res* 1990; 321: 477–94.
2. Uziel G, *et al.* Riboflavin-responsive glutaric aciduria type II presenting as a leukodystrophy. *Pediatr Neurol* 1995; 13: 333–5.
3. Liang W-C, *et al.* Riboflavin-responsive glutaric aciduria type II with recurrent pancreatitis. *Pediatr Neurol* 2004; 31: 218–21.

Migraine. Results from open studies[1,2] and a placebo-controlled trial[3] have suggested that riboflavin in high doses (400 mg daily) might be of some benefit in the prophylaxis of migraine attacks (p. 670.3). However, a controlled study in children found it to be no more effective than placebo.[4]

1. Schoenen J, *et al.* High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. *Cephalalgia* 1994; 14: 328–9.
2. Boehnke C, *et al.* High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. *Eur J Neurol* 2004; 11: 475–7.
3. Schoenen J, *et al.* Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial. *Neurology* 1998; 50: 466–70.
4. MacLennan SC, *et al.* High-dose riboflavin for migraine prophylaxis in children: a double-blind, randomized, placebo-controlled trial. *J Child Neurol* 2008; 23: 1300–4.

Adverse Effects and Precautions

Large doses of riboflavin result in a bright yellow discoloration of the urine that may interfere with certain laboratory tests.

Breast feeding. Supplementation significantly increased riboflavin concentration in the breast milk of women compared with those not given riboflavin. Significant differences between the two groups decreased over the period from 1 to 6 weeks postpartum; both groups of women had breast milk concentrations above previously reported normal values, and the authors concluded that supplementation was not necessary in healthy, well-nourished women.[1] The American Academy of Pediatrics considers the use of riboflavin to be usually compatible with breast feeding.[2]

1. Nail PA, *et al.* The effect of thiamin and riboflavin supplementation on the level of those vitamins in human breast milk and urine. *Am J Clin Nutr* 1980; 33: 198–204.
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 09/01/06)

Pharmacokinetics

Riboflavin is readily absorbed from the gastrointestinal tract. Although riboflavin is widely distributed to body tissues little is stored in the body.

Riboflavin is converted in the body to the coenzyme flavine mononucleotide (FMN; riboflavin 5′-phosphate) and then to another coenzyme flavine adenine dinucleotide (FAD). About 60% of FMN and FAD are bound to plasma proteins. Riboflavin is excreted in urine, partly as metabolites. As the dose increases, larger amounts are excreted unchanged. Riboflavin crosses the placenta and is distributed into breast milk.

Human Requirements

The riboflavin requirement is often related to the energy intake but it appears to be more closely related to resting metabolic requirements. A daily dietary intake of about 1.1 to 1.8 mg of riboflavin is recommended. Liver, kidney, fish, eggs, milk, cheese, yeast, and some green vegetables such as broccoli and spinach are the richest sources of riboflavin. In general, little loss of riboflavin occurs during cooking, but considerable losses may occur if foods, especially milk, are exposed to sunlight.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published for riboflavin[1] and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females of varying ages, and for pregnant and lactating women; the differences between age groups are intended to reflect the changes in caloric intakes at these ages. In the UK the reference nutrient intake (RNI) is 1.3 mg daily and 1.1 mg daily for adult males and females respectively; the estimated average requirement (EAR) is 1.0 mg daily and 900 micrograms daily respectively. In the USA the RDAs for adult males and females are 1.3 and 1.1 mg daily respectively.

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 thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Berivine; Ribon; *China*: Liluokang (利络康); *Fr.*: Beflavine; *Ger.*: B2-ASmedic; *Hong Kong*: FAD Ophthalmic Soln; Hibon; Ribovit†; Super B2†; *India*: Lipabol; *Indon.*: Alinamin; *Israel*: UV-X-Ribo-Dextran; *Thai.*: Biovit B2; Boflavin; Flavin; Tebovin; Vitabee-2-25; *USA*: B_2-400; Cyto B2.

Multi-ingredient Preparations. *Arg.*: Anemidox; Cistidac; Goteborg; Lociherp Liposomas Vitaminado; *Austral.*: Antioxidant Forte Tablets†; Antioxidant Tablets†; Bilberry Plus Eye Health†; Extralife Eye-Care†; Methyl Transfer; PM Eye Tonic; PM IQShield; *Braz.*: Apevinat BC; Frutoplex; Frutovena; Organoneuro Optico; Pre-Mens; *Chile*: Becomplina Fuerte†; Benutrex 1000†; Rodepan; *China*: Kai Yu (凯渝); Norpin A (纳尔平); *Cz.*: Calcium Pharmavit; *Fr.*: Lero Pervulane; *Ger.*: Floradix Eisen-Folsaure; Floradix Krauterblut†; *Gr.*: Arkadin; Lentamine; *Hong Kong*: PM Eye Tonic†; *India*: Aglozyme; Alurazyme; Aminorich; Aneudox-12; Atpro; Carbo Plus; Folnet; Folvina; Ginkoriv Plus; HB-Norm; Hepa-Merz†; Hepawin; Idiglobin; Ipreg; Livosil-B; Lornit; Neurophosphates†; Neurotrat; Oraflora; Ornipan; *Indon.*: Combiplex; Dansera; Dialac; Matase; My Caps; nutrivision; Oculex; Oculex; Reticopen; Retop; Tonikum Bayer; Vitanox; Vitop; Yeastafort; *Irl.*: Quiet Life; *Ital.*: Facovit; Fosforilasi; *Jpn*: Neurovitan; *Malaysia*: P-Trovite; *Mex.*: Pangavit Pediatrico; *Philipp.*: Fer-Essence; Foramefer; Godex; Hanizyn; Hemovin; Heralink; Mitocore; Mitonerb; Mivex; Nakaron; *Pol.*: Biovision; *Rus.*: Corylip (Корилип); Cytoflavin (Цитофлавин); Essliver Forte (Эссливер Форте); Multi-Tabs B-Complex (Мульти-Табс В-Комплекс); *Singapore*: Alinamin-F; Beafort; Beaplex; Ferbeaplex; Gin-Vita; Nutrivision†; *Spain*: Aftasone B C†; *Thai.*: Alinamin-F; B-100 Complex; Neuviplex; Polyvit; Vita-Cal; *Turk.*: Neuvitan; *UK*: Pilfood; Quiet Life; Se-Power; *Ukr.*: B-Complex Multi-Tabs (В-Комплекс Мульти-Табс)†; Cytoflavin (Цитофлавин); Decamevit (Декамевит); Fenules (Фенюльс)†; Fitoval Capsules (Фитовал капсулы); Hepadif (Гепадиф); Hepaforte (Гепафорте); Levasil (Левасил); Neiron (Нейрон); Neurovitan (Нейровитан); Vitrum Foreyes Forte (Витрум Форайс Форте); Vitrum Memory (Витрум Меморн); *USA*: L-Methyl-MC; REQ49+.

Pharmacopoeial Preparations

BP 2014: Vitamins B and C Injection;

BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;

USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; 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; Riboflavin Injection; Riboflavin Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Vitamin B_6 Substances

Vitamina B_6; Витамины Группы B_6

Vitamin B_6 is usually available as pyridoxine but the term is also used to refer to the related compounds, pyridoxal and pyridoxamine.

Metadoxine

Metadoxina; Pyridoxine Pidolate.

Pyridoxine *l*-5-oxopyrrolidine-2-carboxylate.

$C_8H_{11}NO_3$, $C_5H_7NO_3$=298.3

CAS — 74536-44-0.

UNII — EJQ7M98H5J.

Pyridoxal Phosphate

Codecarboxylase; MC-I; Piridoxal, fosfato de; Pyridoxal 5-Phosphate; Пиридоксальфосфат.

3-Hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde 5′-phosphate.

$C_8H_{10}NO_6P$=247.1

CAS — 54-47-7.

ATC — A11HA06.

ATC Vet — QA11HA06.

UNII — 5V5IOJ8338 (pyridoxal phosphate monohydrate); F06SGE49M6 (pyridoxal phosphate).

Pyridoxamine Hydrochloride

Piridoxamina, hidrocloruro de; Pyridoxamine Dihydrochloride; Пиридоксамина Гидрохлорид.

4-Aminomethyl-5-hydroxy-6-methyl-3-pyridinemethanol hydrochloride.

$C_8H_{12}N_2O_2$,2HCl=241.1

CAS — 524-36-7.

UNII — YQ8NCR7V0O.

Pyridoxine Hydrochloride *(BANM, rINNM)*

Adermine Hydrochloride; Hidrocloruro de adermina; Hidrocloruro de piridoxina; Piridoksin Hidroklorür; Piridoksino hidrochloridas; Piridossina Cloridrato; Piridoxina, hidrocloruro de; Piridoxin-hidroklorid; Pirydoksyny chlorowodorek; Pyridoksiinihydrokloridi; Pyridoxine, Chlorhydrate de; Pyridoxinhydrochlorid; Pyridoxin-hydrochlorid; Pyridoxinhydroklorid; Pyridoxini hydrochloridum; Pyridoxinii Chloridum; Pyridoxinium Chloride; Pyridoxol Hydrochloride; Vitamin B_6; Vitamina B_6; Пиридоксина Гидрохлорид.

3-Hydroxy-4,5-bis(hydroxymethyl)-2-picoline hydrochloride.

$C_8H_{11}NO_3$,HCl=205.6

CAS — 65-23-6 (pyridoxine); 58-56-0 (pyridoxine hydrochloride).

ATC — A11HA02.

ATC Vet — QA11HA02.

UNII — 68Y4CF58BV.

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

Ph. Eur. 8: (Pyridoxine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 2.4 to 3.0. Protect from light.

USP 36: (Pyridoxine Hydrochloride). White or practically white crystals or crystalline powder. Soluble 1 in 5 of water and 1 in 115 of alcohol; insoluble in ether. Its solutions in water have a pH of about 3. Store in airtight containers. Protect from light.

Uses and Administration

Pyridoxine, a water-soluble vitamin, is involved mainly in amino acid metabolism, but is also involved in carbohydrate and fat metabolism. It is also required for the formation of haemoglobin.

Deficiency of pyridoxine is rare in humans because of its widespread distribution in foods. Pyridoxine deficiency may however be drug-induced and can occur, for instance, during isoniazid therapy. Inadequate utilisation of pyridoxine may result from certain inborn errors of metabolism. Pyridoxine deficiency may lead to anaemia, dermatitis, cheilosis, and neurological symptoms such as peripheral neuritis, and convulsions.

Pyridoxine is used in the treatment and prevention of pyridoxine deficiency states. It is usually given orally, the preferred route, but may also be given by the subcutaneous, intramuscular, or intravenous routes. Doses of pyridoxine hydrochloride up to 150 mg daily are used in general deficiency states; higher doses of up to 400 mg daily are used in the treatment of sideroblastic anaemias (see p. 2106.1); and similar high doses have been used to treat certain

metabolic disorders such as homocystinuria (see Amino Acid Metabolic Disorders, below) or primary hyperoxaluria (below). Pyridoxine has also been used to treat seizures due to hereditary syndromes of pyridoxine deficiency or dependency in infants.

Pyridoxine has also been tried in the treatment of many other disorders, including depression and other symptoms associated with the premenstrual syndrome (see below) and the use of oral contraceptives, although its efficacy has been questioned. Pyridoxine hydrochloride is used, as a modified-release combination preparation with doxylamine succinate, in the management of nausea and vomiting of early pregnancy; see under Doxylamine Succinate, p. 627.3, for details of doses.

Pyridoxine is usually given as the hydrochloride although other salts such as the citrate, oxoglurate, phosphate, and phosphoserinate, have also been used. Metadoxine, the pidolate, has been investigated in alcoholism (see below).

For the use of pyridoxine in the prophylaxis of isoniazid-induced peripheral neuritis and for the treatment of acute isoniazid toxicity, see Treatment of Adverse Effects, under Isoniazid, p. 312.3.

Pyridoxal phosphate may be used to treat vitamin B_6 deficiency. Pyridoxamine has also been given.

Reviews.

1. Bender DA. Non-nutritional uses of vitamin B_6. *Br J Nutr* 1999; 81: 7–20.
2. Lheureux P, *et al.* Pyridoxine in clinical toxicology: a review. *Eur J Emerg Med* 2005; 12: 78–85.

Administration in children. For doses of pyridoxine in the management of children with **amino acid metabolic disorders** and **pyridoxine-dependent seizures** see below.

Pyridoxine may also be used to treat or prevent **isoniazid-induced neuropathy**. For doses in children see Treatment of Adverse Effects, under Isoniazid, p. 312.3.

Alcoholism and alcohol poisoning. Pyridoxine and its pidolate, known as metadoxine, have been tried in the treatment of alcohol poisoning and alcoholism.[1] One study showed pyridoxine to be ineffective in acute alcohol poisoning[2] but another[3] suggested that the pidolate might be of benefit as an adjunct in the management of alcohol withdrawal (p. 1734.1). In patients treated for alcoholic fatty liver, liver function returned to normal more quickly with metadoxine, even in patients who did not completely abstain from alcohol.[4]

1. Addolorato G, *et al.* Metadoxine in the treatment of acute and chronic alcoholism: a review. *Int J Immunopathol Pharmacol* 2003; 16: 207–14.
2. Mardel S, *et al.* Intravenous pyridoxine in acute ethanol intoxication. *Hum Exp Toxicol* 1994; 13: 321–3.
3. Rizzo A, *et al.* Uso terapeutico della metadoxina nell'alcolismo cronico: studio clinico in doppio cieco su pazienti ricoverati in un reparto di medicina generale. *Clin Ter* 1993; 142: 243–50.
4. Caballería J, *et al.* Metadoxine accelerates fatty liver recovery in alcoholic patients: results of a randomized double-blind, placebo-control trial. *J Hepatol* 1998; 28: 54–60.

Amino acid metabolic disorders. Pyridoxine has been used in various inborn errors of amino acid metabolism, such as homocystinuria (p. 2042.2), with or without cobalamins and folate. Relatively high doses may need to be given (see Uses and Administration, p. 2105.3). For children with metabolic disorders such as homocystinuria and cystathioninuria, the *BNFC* suggests pyridoxine in an oral dose of 50 to 100 mg once or twice daily for neonates, and 50 to 250 mg once or twice daily in patients aged 1 month to 18 years. For the use of pyridoxine in primary hyperoxaluria, another inherited metabolic disorder, see below.

Anaemias. Some patients with acquired or hereditary sideroblastic anaemia (p. 1123.1) that is severe enough to require treatment will respond to high doses (up to 400 mg daily) of pyridoxine, and a trial is considered worthwhile in all patients.

Cardiovascular disease. For mention of the possible link between vitamin B_6, hyperhomocysteinaemia, and cardiovascular disease, see under Folic Acid, p. 2063.3. Pyridoxal phosphate is thought to prevent cellular calcium overload in ischaemia-reperfusion injury, but a large multicentre study[1] investigating doses of 250 mg daily orally given 3 to 10 hours before coronary artery bypass graft surgery in intermediate- to high-risk patients, and for a further 30 days after the procedure, found it did not reduce the incidence of cardiovascular death or non-fatal myocardial infarction.

1. Alexander JH, *et al.* MEND-CABG II Investigators. Efficacy and safety of pyridoxal 5'-phosphate (MC-1) in high-risk patients undergoing coronary artery bypass graft surgery: the MEND-CABG II randomized clinical trial. *JAMA* 2008; 299: 1777–87.

Carpal tunnel syndrome. Pyridoxine has been advocated by some[1] for patients with carpal tunnel syndrome (see Soft-tissue Rheumatism, p. 14.2), but evidence of efficacy is considered to be limited.[2] In most studies reporting improvement with pyridoxine, doses have ranged from 50 to 300 mg daily for 12 weeks; a review concluded that treatment should be stopped if there is no apparent response after this period.[3]

1. Lewis PJ. Pyridoxine supplements may help patients with carpal tunnel syndrome. *BMJ* 1995; 310: 1534.
2. O'Connor D, *et al.* Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2003 (accessed 09/01/06).
3. Aufiero E, *et al.* Pyridoxine hydrochloride treatment of carpal tunnel syndrome: a review. *Nutr Rev* 2004; 62: 96–104.

Epilepsy. Pyridoxine-dependent epilepsy is an autosomal recessive disorder associated with decreased central γ-aminobutyric acid (GABA) concentrations and elevated cerebral glutamate concentrations. Untreated patients suffer from progressive encephalopathy, mental retardation, and intractable epilepsy; lifelong supplementation with pyridoxine can control epileptic symptoms but mental retardation may still develop. An epidemiological study[1] defined cases as those children with recurrent seizures that ceased within 7 days of oral pyridoxine at a usual dose of 30 mg/kg daily (minimum dose 15 mg/kg daily; maximum dose 1 g/kg daily), or within 30 minutes of intravenous pyridoxine (usual dose 100 mg; minimum dose 50 mg), that recurred when supplementation was withdrawn, and ceased again upon dosage as before. The study found that, despite their rarity, pyridoxine-dependent seizures frequently present atypically, and the author suggested that pyridoxine be given to all children with intractable seizures beginning before 3 years of age, including neonates with suspected hypoxic-ischaemic encephalopathy.

Test doses of pyridoxine intravenously, repeated at intervals of 10 minutes up to a total of 500 mg if necessary, have been suggested in the diagnosis of pyridoxine-dependent epilepsy; if the patient responds then a daily oral dose of 5 mg/kg is suggested although there is no real consensus on the appropriate dosage.[2] The *BNFC* suggests an intravenous test dose of 50 to 100 mg; in those who respond, oral doses of 50 to 100 mg once daily in neonates or 20 to 50 mg once or twice daily in older children (in whom up to 30 mg/kg or 1 g daily has been used), are suggested, adjusted as required. Alternatively, in patients with recurrent seizures refractory to conventional anticonvulsant therapy, oral pyridoxine supplementation of 15 mg/kg daily should lead to resolution of clinical seizures within a week in those with the condition; however, in some patients the daily dose required may be lower.[3]

A study in one patient[4] found that although pyridoxine 5 mg/kg reduced glutamate concentrations in CSF from the untreated value of 200 times normal limits, it did so only to 10 times the normal value, despite remission of symptoms. Doses of 10 mg/kg daily were required to normalise CSF glutamate, and it was suggested that this was a more appropriate target for therapy. In some children, pyridoxal phosphate has been suggested to be more effective than pyridoxine in controlling seizures.[5]

1. Baxter P. Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. *Arch Dis Child* 1999; 81: 431–3.
2. Gospe SM. Current perspectives on pyridoxine-dependent seizures. *J Pediatr* 1998; 132: 919–23.
3. Gospe SM. Pyridoxine-dependent seizures: findings from recent studies pose new questions. *Pediatr Neurol* 2002; 26: 181–5.
4. Baumeister FAM, *et al.* Glutamate in pyridoxine-dependent epilepsy: neurotoxic glutamate concentration in the cerebrospinal fluid and its normalization by pyridoxine. *Pediatrics* 1994; 94: 318–21.
5. Wang H-S, *et al.* Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. *Arch Dis Child* 2005; 90: 512–15.

Palmar-plantar erythrodysesthesia syndrome. Pyridoxine, in doses of 100 to 300 mg daily, has been used successfully[1] for treating and preventing palmar-plantar erythrodysesthesia syndrome associated with antineoplastic therapy (see p. 730.1).

1. Nagore E, *et al.* Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome: incidence, recognition and management. *Am J Clin Dermatol* 2000; 1: 225–34.

Premenstrual syndrome. Pyridoxine has been widely used in the premenstrual syndrome (p. 2272.3) despite controversy over its effectiveness. Some consider that depressive symptoms may be provoked by pyridoxine deficiency because of its role as a coenzyme in the production of certain neurotransmitters, but it is difficult to attribute any of the other symptoms of the premenstrual syndrome to pyridoxine deficiency and doses of 50 mg are no more effective than a placebo.[1] A systematic review found that although treatment with pyridoxine was more effective than placebo, there was insufficient high-quality evidence to recommend its routine use in premenstrual syndrome.[2] If pyridoxine is used, the dosage should be restricted (see Effects on the Nervous System, below) because of concerns about neurotoxicity.[3] Although unlicensed in the UK, the *BNF* suggests an oral pyridoxine dose of 50 to 100 mg daily for premenstrual syndrome.

1. West CP. The premenstrual syndrome. *Prescribers' J* 1987; 27 (2): 9–15.
2. Wyatt KM, *et al.* Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ* 1999; 318: 1375–81.
3. Severino SK, Moline ML. Premenstrual syndrome: identification and management. *Drugs* 1995; 49: 71–82.

Primary hyperoxaluria. Primary hyperoxaluria (as distinct from the various forms secondary to other disorders) is a genetic disorder characterised by excessive synthesis and urinary excretion of oxalic acid. Two forms are known, type I (hyperglycolic aciduria) and type II (L-glyceric aciduria), associated with different enzyme defects. They are marked by recurrent calcium oxalate kidney stones, or nephrocalcinosis, leading to renal failure together with extrarenal deposition of calcium oxalate and frequently severe peripheral vascular insufficiency. Treatment with high doses of pyridoxine may help decrease oxalate excretion particularly in type I disease,[1,2] although response is variable.[3] A few patients may respond to lower (physiological) doses.[4] Such treatment can be used with an oral orthophosphate supplement, which helps reduce renal deposition of calcium oxalate, and the combination appears to preserve renal function.[5] Therapy with magnesium salts, potassium citrate, and thiazide diuretics has also been suggested.[2] In patients in whom renal failure develops, the results of kidney transplantation have been disappointing, due to deposition of calcium oxalate in the new kidney, although transplanting the liver as well can correct the enzyme defect.[1,6] Pre-emptive liver transplantation, performed before renal failure or systemic oxalosis has occurred, may be an option.[2]

1. Cochat P, Basmaison O. Current approaches to the management of primary hyperoxaluria. *Arch Dis Child* 2000; 82: 470–3.
2. Marangella M, *et al.* The primary hyperoxaluries. *Contrib Nephrol* 2001; 134: 11–32.
3. Toussaint C. Pyridoxine-responsive PH1: treatment. *J Nephrol* 1998; 1 (suppl 1): 49–50.
4. Yendt ER, Cohanim M. Response to a physiologic dose of pyridoxine in type I primary hyperoxaluria. *N Engl J Med* 1985; 312: 953–7.
5. Milliner DS, *et al.* Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. *N Engl J Med* 1994; 331: 1553–8.
6. Watts RWE, *et al.* Combined hepatic and renal transplantation in primary hyperoxaluria type I: clinical report of nine cases. *Am J Med* 1991; 90: 179–88.

Tardive dyskinesia. In a double-blind, controlled, cross-over study,[1] daily oral doses of vitamin B_6 1.2 g effectively reduced the symptoms of tardive dyskinesia (see Extrapyramidal Disorders, p. 1049.2).

1. Lerner V, *et al.* Vitamin B_6 treatment for tardive dyskinesia: a randomized, double-blind, placebo-controlled, crossover study. *J Clin Psychiatry* 2007; 68: 1648–54.

Adverse Effects and Precautions

Long-term use of large doses of pyridoxine is associated with the development of severe peripheral neuropathies; the dose at which these occur is controversial (see Effects on the Nervous System, below).

Breast feeding. Vitamin B_6 is excreted into breast milk.[1,2] While some have expressed concern over the inhibition of breast milk secretion by pyridoxine,[3] others have cautioned that pyridoxine deficiency may cause seizures in the neonate.[4] The American Academy of Pediatrics considers the use of pyridoxine to be usually compatible with breast feeding.[5]

1. West KD, Kirksey A. Influence of vitamin B_6 intake on the content of the vitamin in human milk. *Am J Clin Nutr* 1976; 29: 961–9.
2. Roepke JLB, Kirksey A. Vitamin B_6 nutriture during pregnancy and lactation: 1. Vitamin B_6 intake, levels of the vitamin in biological fluids, and condition of the infant at birth. *Am J Clin Nutr* 1979; 32: 2249–56.
3. Greentree LB. Dangers of vitamin B_6 in nursing mothers. *N Engl J Med* 1979; 300: 141–2.
4. Lande NL. More on dangers of vitamin B_6 in nursing mothers. *N Engl J Med* 1979; 300: 926–7.
5. 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 09/01/06)

Effects on the nervous system. Severe sensory neuropathy has been described in patients receiving large doses of pyridoxine (2 to 6 g daily) for periods of 2 to 40 months.[1] There has, however, been debate as to whether smaller doses can produce such effects. Some contend that amounts of pyridoxine below this level are unlikely to produce toxic effects.[2,3] However, there have been some case reports[4,5] with amounts up to about 500 mg daily and prolonged use of even lower doses (about 200 mg daily or less) may also cause sensory peripheral neuropathy.[6,7] After a review of the possible toxicity associated with lower doses of pyridoxine, proposals were put forward in the UK to limit the dose freely available in dietary supplements to 10 mg daily; products supplying up to 50 mg daily would continue to be available from pharmacies and higher doses would only be available on prescription.[8] These proposals were heavily contested.[8,9] An upper level of intake of 50 mg daily is recommended in Australia,[7]

whereas an upper limit of 100 mg daily has been suggested in the USA.[9]

1. Schaumburg H, *et al.* Sensory neuropathy from pyridoxine abuse: a new megavitamin syndrome. *N Engl J Med* 1983; 309: 445–8.
2. Pauling L. Sensory neuropathy from pyridoxine abuse. *N Engl J Med* 1984; 310: 197.
3. Baker H, Frank O. Sensory neuropathy from pyridoxine abuse. *N Engl J Med* 1984; 310: 197.
4. Berger A, Schaumburg HH. More on neuropathy from pyridoxine abuse. *N Engl J Med* 1984; 311: 986.
5. Waterston JA, Gilligan BS. Pyridoxine neuropathy. *Med J Aust* 1987; 146: 640–2.
6. Dordain G, Deflond D. Neuropathies à la pyridoxine: revue de la littérature. *Therapie* 1994; 49: 333–7.
7. Adverse Drug Reactions Advisory Committee (ADRAC). High-dose vitamin B6 may cause peripheral neuropathy. *Aust Adverse Drug React Bull* 2008; 27: 14–15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0808.pdf (accessed 26/01/09)
8. Collier J. Vitamin B-6: food or medicine? *BMJ* 1998; 317: 92–3.
9. Anonymous. Still time for rational debate about vitamin B_6. *Lancet* 1998; 351: 1523.

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Pyridoxine reduces the effects of levodopa (see p. 908.1), but this does not occur if a dopa decarboxylase inhibitor is also given. Pyridoxine reduces the activity of altretamine. It has also been reported to decrease serum concentrations of phenobarbital (p. 538.1) and phenytoin (p. 545.2). Many drugs may increase the requirements for pyridoxine; such drugs include hydralazine, isoniazid, penicillamine, and oral contraceptives.

Pharmacokinetics

Pyridoxine, pyridoxal, and pyridoxamine are readily absorbed from the gastrointestinal tract after oral doses and are converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. They are stored mainly in the liver where there is oxidation to 4-pyridoxic acid and other inactive metabolites which are excreted in the urine. As the dose increases, proportionally greater amounts are excreted unchanged in the urine. Pyridoxal crosses the placenta and is distributed into breast milk.

Human Requirements

For adults, the daily requirement of pyridoxine is probably about 1.5 to 2 mg and this amount is present in most normal diets. The requirement tends to increase as protein intake increases due to the role of the vitamin in amino acid metabolism. Meats, especially chicken, kidney, and liver, cereals, eggs, fish, and certain vegetables and fruits are good sources of pyridoxine.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p. 2046.1) have been published for vitamin B_6 and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and during pregnancy and lactation. In the UK the reference nutrient intake (RNI) is 15 micrograms per g of protein daily for adult males and females and the estimated average requirement (EAR) is 13 micrograms per g of protein daily for the same group. In the USA the RDA for adult men ranges from 1.3 to 1.7 mg daily and that for adult women ranges from 1.3 to 1.5 mg daily.[2] The tolerable upper intake level is 100 mg daily.[2] The Expert Group on Vitamins and Minerals[3] have established a safe upper level (SUL) for vitamin B_6 of 170 micrograms/kg daily. For recommended limits in dietary supplements see Effects on the Nervous System, p. 2106.3.

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. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 09/01/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Benadon; *Austral.*: Pyroxin; *Belg.*: Bedoxine†; *Braz.*: Ponto-Vit B6†; Metadoxil; Neuri B6; Seis-B; *Canad.*: B-natal; *Chile*: Vitabe; *China*: Fei Li Gu (菲力古); GanXin (甘忻); Hao Qiang (昊强); Jie Ao (洁傲); Shen Kai Neng (申凯能); Xin Li De (欣立得); *Denm.*: BiOrto B6; Super B6; *Fin.*: Heksavit†; Vita-B6; *Fr.*: Becilan; Dermo 6; *Ger.*: B6-ASmedic; B_6 Vicotrat; Bonasanit†; Novirell B_6; *Gr.*: Becilan; Benadon; Besix; Bexivit; *Hong Kong*: Pyrlbion†; Pyrixin†; Super B6†; *Hung.*: Beres B6; Peroglobin-B12; Metadoxil; *India*: Abix; Alcoliv; Benadon; Cobal Forte; Ingavit B6; Metadoxil; Pyricontin; *Indon.*: Liconam; Stopmun†; *Irl.*: Compliment†; *Israel*: Anacrodyne; B-Six; *Ital.*: Benadon; Metadoxil; Xanturenasi; *Malaysia*: Upha B6; *Mex.*: Abrixone; Fortical: Metasin; Valparina†; *Philipp.*: Drexabion; Hybutin; Jaga; Lixtress; Meganerv; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Pyricar; Supraneuron; Vineuron; *Port.*: Benadon; *Rus.*: Metadoxil (Метадоксил); Vitagamma (Витагамма); *S.Afr.*: Beesix†; Lactosec; *Spain*: Benadon; Conductasa; *Swed.*: Benadon†; *Switz.*: Benadon; *Thal.*: B Six P; B-6; B6-50; Besix; Biovit B6; Jotexin; Mega-B; Metadoxil; *Turk.*: B_6 Vigen; Libavit B_6; Postadoxine; *Venez.*: Beplus; Biprin; Clodoxin; Suprabion.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. *Canad.*: Isotamine B; *Ger.*: Isozid comp N; tebesium; *Hong Kong*: Trisofort†; *India*: Becox RH; Bicox Kid; Binex; Caviter FD; Cx-3; Cx-4; Cx-5; Cocox Compound; Isokin-300; Mycodot Kit; Mycodot-4; Mycodot-E; Mycodot-Z; Rifa E: Rifa; Wokex-2; Wokex-3; Wokex-4; *Indon.*: bacbutINH; Erabutol Plus; INH-Ciba; INHA; Inoxin; Kapedoxin; Medinih-OD†; Meditam-6†; Mycothambin-INH†; Niacifort-6; Niazitol; Pehadoxin; Pulmolin†; Pulna; Pyravit; Pyrifort†; Santibi Plus; Suprazid; TB Vit 6; *Ital.*: Etanicozid B6; *Philipp.*: CombiKids†; Comprilex; Curazid (Reformulated); Ethamizid; Ethi 400; Eurocoxin: Isodexid; Isoprim; Isoxin; Kidz Kit 2; Kidz Kit 3; Nicetal†; Odinah; Pulmodrin; Refam Duo†; Refam Pedia Kit†; Sthamizide; SVM-Polypac-A†; Techxafort; Terozid; Trisofort†; Vamsoxid†; *Pol.*: Laktomag B_6; *Rus.*: Coxerin Plus (Коксерин Плюс); Cyclo Plus (Цикло Плюс); Isocomb (Изокомб); Isozid Comp (Изозид Комп); Laslonvita (Ласлонвита); Lomecomb (Ломекомб); Protiocomb (Протиокомб); Protub-2 (Протуб-2); Protub-5 (Протуб-5); Protub-Lome (Протуб-Ломе); Protubvita (Протубвита); Repin B_6 (Репин B_6); Rezonisate Plus (Резонизат Плюс); Rifacomb (Рифакомб); Tubavit (Тубавит); *Spain*: Cemidon B6; Tisobrif†; *Turk.*: Isovit.

Homoeopathic Preparations. *Ger.*: Infi-Symphytum; NeyFoc Nr 69; NeyGero Nr 64; NeyGeront Vitalkapsein A.

Pharmacopoeial Preparations

BP 2014: Pyridoxine Tablets; Vitamins B and C Injection;
BPC 1973: Strong Compound Vitamin B Tablets;
USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; 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; Pyridoxine Hydrochloride Injection; Pyridoxine Hydrochloride Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Vitamin B_{12} Substances

Vitamina B_{12}; Витамины Группы B_{12}.

Vitamin B_{12} is the name generally used for a group of related cobalt-containing compounds, also known as cobalamins, of which cyanocobalamin and hydroxocobalamin are the principal forms in clinical use.

Cobamamide *(pINN)*

Adenosylcobalamin; Cobamamida; Cobamamidum; Coenzyme B_{12}; Dibencozide; Dibenzocozamide; Dimebenzocozamide; Kobamamid; Кобамамид.

Inner salt of the Co-(5′-deoxyadenosine-5′) derivative of the 3′-ester of cobinamide phosphate with 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole.

$C_{72}H_{100}CoN_{18}O_{17}P$=1579.6
CAS — 13870-90-1.
ATC — B03BA04.
ATC Vet — QB03BA04.

Pharmacopoeias. In *Chin.*

Cyanocobalamin *(BAN, rINN)*

Cianocobalamina; Cianokobalamin; Cianokobalaminas; Cobamin; Cyanocobalamine; Cyanocobalaminum; Cyanokobalamin; Cycobemin; Cyjanokobalamina; Kyanokobalamin; Siyanokobalamin; Syanokobalamiini; Цианокобаламин.

Coα-[α-(5,6-Dimethylbenzimidazolyl)]-Coβ-cyanocobamide.

$C_{63}H_{88}CoN_{14}O_{14}P$=1355.4
CAS — 68-19-9.
ATC — B03BA01.
ATC Vet — QB03BA01.
UNII — P6YC3EG204.

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

Ph. Eur. 8: (Cyanocobalamin). A dark red, crystalline powder or dark red crystals. The anhydrous substance is very hygroscopic. Sparingly soluble in water and in alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light.

USP 36: (Cyanocobalamin). Dark red crystals or amorphous or crystalline red powder. In the anhydrous form it is very hygroscopic and when exposed to air it may absorb about 12% of water. Soluble 1 in 80 of water; soluble in alcohol; insoluble in acetone, in chloroform, and in ether. Store in airtight containers. Protect from light.

Hydroxocobalamin *(BAN, USAN, rINN)*

Hidroksokobalamin; Hidroxocobalamina; Hydroksikobalamiini; Hydroxikobalamin; Hydroxocobalamine; Hydroxocobalaminum; Hydroxycobalaminum; Idrossocobalamina; Гидроксокобаламин.

Coα-[α-(5,6-Dimethylbenzimidazolyl)]-Coβ-hydroxocobamide.

$C_{62}H_{89}CoN_{13}O_{15}P$=1346.4
CAS — 13422-51-0.
ATC — B03BA03; V03AB33.
ATC Vet — QB03BA03; QV03AB33.
UNII — Q40X8H422O.

NOTE. The hydrated form of hydroxocobalamin has been referred to as aquocobalamin.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Hydroxocobalamin). Dark red crystals or red crystalline powder. Is odourless or has not more than a slight acetone odour. The anhydrous form is very hygroscopic. Soluble 1 in 50 of water and 1 in 100 of alcohol; practically insoluble in acetone, in chloroform, in ether, and in benzene; sparingly soluble in methyl alcohol. pH of a 2% solution in water is between 8.0 and 10.0. Store in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Hydroxocobalamin Acetate *(BANM, rINNM)*

Acetato de hidroxocobalamina; Acetatocobalamin; Hidroksokobalamino acetatas; Hidroxocobalamina, acetato de; Hidroxokobalamin-acetát; Hydroksokobalamiinisetaatti; Hydroxocobalaminacetat; Hydroxocobalamine, Acétate d'; Hydroxocobalamini acetas; Hydroxokobalamin acetát; Hydroxokobalaminacetat; Гидроксокобаламина Ацетат.

$C_{64}H_{93}CoN_{13}O_{17}P$=1406.4
CAS — 22465-48-1.
UNII — 5535M27N3Q.

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

Ph. Eur. 8: (Hydroxocobalamin Acetate). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble in water. Some decomposition may occur on drying. Store at a temperature between 2 degrees and 8 degrees in airtight containers. Protect from light.

Hydroxocobalamin Chloride *(BANM, rINNM)*

Cloruro de hidroxocobalamina; Hidroksokobalamino chloridas; Hidroxocobalamina, cloruro de; Hidroxokobalaminklorid; Hydroksokobalamiinikloridi; Hydroxocobalamine, Chlorure d'; Hydroxocobalaminhydrochlorid; Hydroxocobalamini chloridum; Hydroxocobalamini Hydrochloridum; Hydroxokobalamin hydrochlorid; Hydroxokobalaminklorid; Гидроксокобаламина Хлорид.

$C_{62}H_{90}ClCoN_{13}O_{15}P$=1382.8

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

Ph. Eur. 8: (Hydroxocobalamin Chloride). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble in water. Some decomposition may occur on drying. Store at a temperature between 2 degrees and 8 degrees in airtight containers. Protect from light.

Hydroxocobalamin Sulfate *(BANM, rINNM)*

Hidroksokobalamino sulfatas; Hidroxocobalamina, sulfato de; Hidroxokobalamin-szulfát; Hydroksokobalamiinisulfaatti; Hydroxocobalamin Sulphate; Hydroxocobalamine, Sulfate d'; Hydroxocobalamini Sulfas; Hydroxocobalaminsulfat; Hydroxokobalamin sulfát; Hydroxokobalaminsulfat; Sulfato de hidroxocobalamina; Гидроксокобаламина Сульфат.

$C_{124}H_{180}Co_2N_{26}O_{34}P_2S$=2790.8

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

Ph. Eur. 8: (Hydroxocobalamin Sulfate). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble

in water. Some decomposition may occur on drying. Store at a temperature between 2 degrees and 8 degrees in airtight containers. Protect from light.

Mecobalamin *(BAN, USAN, pINN)*

Mecobalamina; Mécobalamine; Mecobalaminum; Methylcobalamin; Мекобаламин.

Coα-[α-(5,6-Dimethylbenzimidazolyl)]-Coβ-methylcobamide.

$C_{63}H_{91}CoN_{13}O_{14}P$=1344.4.

CAS — 13422-55-4.

ATC — B03BA05.

ATC Vet — QB03BA05.

UNII — BR1SN1JS2W.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Vitamin B_{12}, a water-soluble vitamin, occurs in the body mainly as methylcobalamin (mecobalamin) and as adenosylcobalamin (cobamamide) and hydroxocobalamin. Mecobalamin and cobamamide act as coenzymes in nucleic acid synthesis. Mecobalamin is also closely involved with folic acid in several important metabolic pathways.

Vitamin B_{12} deficiency can occur in strict vegetarians with an inadequate dietary intake, although it may take many years before a deficiency is produced. Deficiency is more likely in patients with malabsorption syndromes or metabolic disorders, nitrous oxide-induced megaloblastosis, or after gastrectomy or extensive ileal resection. Deficiency leads to the development of megaloblastic anaemias and demyelination and other neurological damage. A specific anaemia known as pernicious anaemia develops in patients with an absence of the intrinsic factor necessary for good absorption of the vitamin from dietary sources.

Vitamin B_{12} preparations are used in the treatment and prevention of vitamin B_{12} deficiency. It is essential to identify the exact cause of deficiency, preferably before starting therapy. Hydroxocobalamin is generally preferred to cyanocobalamin; it binds more firmly to plasma proteins and is retained in the body longer (see under Pharmacokinetics, p. 2110.2). Cyanocobalamin and hydroxocobalamin are generally given by the intramuscular route, although cyanocobalamin may be given orally or subcutaneously, or intranasally (see also under Administration, below). Oral cyanocobalamin may be used in treating or preventing vitamin B_{12} deficiency of dietary origin.

In the UK, recommended doses for **pernicious anaemia** and other megaloblastic anaemias are as follows:

- in patients *without neurological involvement* doses are hydroxocobalamin (or cyanocobalamin) 250 to 1000 micrograms intramuscularly on alternate days for 1 to 2 weeks, then 250 micrograms weekly until the blood count returns to normal. Maintenance doses of 1000 micrograms are given every 2 to 3 months as hydroxocobalamin, or monthly as cyanocobalamin
- if there is *neurological involvement*, hydroxocobalamin or cyanocobalamin may be given intramuscularly in doses of 1000 micrograms on alternate days and continued for as long as improvement occurs. Maintenance doses of 1000 micrograms are given every 2 months as hydroxocobalamin, or monthly as cyanocobalamin
- for the *prophylaxis* of anaemia associated with vitamin B_{12} deficiency resulting from gastrectomy or malabsorption syndromes hydroxocobalamin may be given in doses of 1000 micrograms intramuscularly every 2 or 3 months or cyanocobalamin in doses of 250 to 1000 micrograms intramuscularly each month
- for vitamin B_{12} deficiency of *dietary* origin, oral cyanocobalamin 50 to 150 micrograms may be taken daily between meals. For discussion of oral cyanocobalamin therapy for the treatment of pernicious anaemia, see Administration, below

Lower doses of both cyanocobalamin and hydroxocobalamin are recommended for pernicious anaemia in the USA:

- for *treatment*, the usual intramuscular or subcutaneous dose of cyanocobalamin is 100 micrograms daily for 6 or 7 days; if there is a response, a further 7 doses may be given on alternate days, then every 3 to 4 days for 2 to 3 weeks. For hydroxocobalamin the usual intramuscular dose is 30 micrograms daily for 5 to 10 days
- for *maintenance*, monthly injections of cyanocobalamin 100 micrograms (intramuscularly or subcutaneously), or intramuscular hydroxocobalamin 100 to 200 micrograms are given. Intranasal preparations of cyanocobalamin are also available for maintenance therapy in those without neurological involvement. An initial dose of 500 micrograms (as one 500-microgram spray in one nostril) is given once weekly and then adjusted according to response. Alternatively, an initial dose of 50 micrograms (as one 25-microgram spray in each nostril) is given once daily, and can be increased to twice daily if required
- in patients with normal gastrointestinal absorption, oral cyanocobalamin doses of 1 to 25 micrograms daily are considered sufficient as a *dietary supplement* (see also Administration, below)

Treatment of vitamin B_{12} deficiency usually results in rapid haematological improvement and a striking clinical response. However, neurological symptoms respond more slowly and in some cases remission may not be complete.

Cobamamide and mecobalamin may also be used for vitamin B_{12} deficiency.

Hydroxocobalamin may also be given in the treatment of **tobacco amblyopia and Leber's optic atrophy**; initial doses are 1000 micrograms daily for 2 weeks intramuscularly followed by 1000 micrograms twice weekly for as long as improvement is maintained. Thereafter, 1000 micrograms is given every 1 to 3 months.

Hydroxocobalamin is also used for the treatment of known or suspected **cyanide toxicity** (see below). Each 2.5 g vial of hydroxocobalamin is reconstituted with 100 mL of diluent, preferably sodium chloride 0.9%. The starting dose for adults is 5 g intravenously over 15 minutes. Depending on the severity of the toxicity and the clinical response, a second dose of 5 g may be infused over 15 minutes to 2 hours.

For administration in children, see below.

Cyanocobalamin and hydroxocobalamin are also used in the **Schilling test** to investigate vitamin B_{12} absorption and deficiency states. They are given in a non-radioactive form with cyanocobalamin radioactively-labelled with cobalt-57 (p. 2223.3) or cobalt-58 (p. 2223.3) and the amount of radioactivity excreted in the urine can be used to assess absorption status. A differential Schilling test, in which the forms of cyanocobalamin are given under different conditions (such as with intrinsic factor, antibacterials, or pancreatic enzymes) can provide information about the cause of the malabsorption.

Administration. The small amounts of vitamin B_{12} present in the diet are absorbed from the gastrointestinal tract by an active process that involves binding with intrinsic factor. As intrinsic factor is absent in patients who have developed pernicious anaemia it has often been assumed that *oral* vitamin B_{12} preparations will therefore be ineffective. However, about 1% of an oral dose is absorbed by passive diffusion, and with large doses this amount may be sufficient for therapy. Thus attention has been given again to the use of oral cobalamins for the treatment of pernicious anaemia.[1-4] Oral cyanocobalamin 2000 micrograms daily was as effective as intramuscular therapy in patients with vitamin B_{12} deficiency in a comparative study.[5] Some now consider that oral doses of 1000 micrograms daily,[3,6] or every 2 weeks for children,[7] are a suitable alternative to injections given at monthly or so intervals; others still deem oral use to be unjustified on the grounds of negligible oral absorption.[8] A systematic review[9] of 2 studies found some evidence for a satisfactory haematological, biochemical, and clinical short-term response to oral replacement in some patients with conditions associated with malabsorption. Another review[10] concluded that, while there is substantial evidence to support the use of 1000 to 2000 micrograms daily of oral cyanocobalamin as maintenance therapy, parenteral therapy is preferable for initial treatment of those with neurological symptoms. Oral formulations are being developed which use carrier molecules to enhance absorption.

Cyanocobalamin is also effective when given *intranasally*,[11] with peak plasma concentrations greater than those achievable orally, and this may offer another alternative to injection. The intranasal absorption of hydroxocobalamin has been studied.[12,13]

Cyanocobalamin has also been given *sublingually*. Normalisation of serum cobalamin concentration has been reported in 18 patients given sublingual cyanocobalamin 2000 micrograms daily for 7 to 12 days;[14] 500 micrograms sublingually daily was found to be as effective as the same dose given orally in correcting deficiency.[15]

1. Lederle FA. Oral cobalamin for pernicious anemia: medicine's best kept secret? *JAMA* 1991; 265: 94–5.
2. Hathcock JN, Troendle GJ. Oral cobalamin for treatment of pernicious anemia? *JAMA* 1991; 265: 96–7.
3. Elia M. Oral or parenteral therapy for B12 deficiency. *Lancet* 1998; 352: 1721–2.
4. Anonymous. Oral or intramuscular vitamin B_{12}? *Drug Ther Bull* 2009; 47: 19–21.
5. Kuzminski AM, *et al.* Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998; 92: 1191–8.
6. Andrès E, *et al.* Usefulness of oral cyanocobalamin therapy in severe hematologic manifestations related to vitamin B_{12} deficiency. *Ann Pharmacother* 2004; 38: 1086–7.
7. Çetin M, Altay C. Efficacy of oral vitamin B_{12} treatment in children. *J Pediatr* 2001; 139: 754.
8. Van der Kuy P-HM, *et al.* Bioavailability of oral hydroxocobalamin. *Br J Clin Pharmacol* 2000; 49: 395P–396P.
9. Vidal-Alaball J, *et al.* Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 05/09/06).
10. Lane LA, Rojas-Fernandez C. Treatment of vitamin B_{12}-deficienc anemia: oral versus parenteral therapy. *Ann Pharmacother* 2002; 36 1268–72.
11. Romeo VD, *et al.* Intranasal cyanocobalamin. *JAMA* 1992; 268: 1268–9
12. van Asselt DZB, *et al.* Nasal absorption of hydroxocobalamin in health elderly adults. *Br J Clin Pharmacol* 1998; 45: 83–6.
13. Slot WB, *et al.* Normalization of plasma vitamin B12 concentration b intranasal hydroxocobalamin in vitamin B12-deficient patients *Gastroenterology* 1997; 113: 430–3.
14. Delpre G, *et al.* Sublingual therapy for cobalamin deficiency as a alternative to oral and parenteral cobalamin supplementation. *Lancet* 1999; 354: 740–1.
15. Sharabi A, *et al.* Replacement therapy for vitamin B12 deficiency comparison between the sublingual and oral route. *Br J Clin Pharmacol* 2003; 56: 635–8.

Administration in children. In neonates and children up to 18 years with congenital transcobalamin II deficiency the *BNFC* suggests a dose of hydroxocobalamin 1 mg by intramuscular injection given three times weekly. After 1 year this may be reduced to 1 mg once weekly.

In children aged from 1 month with megaloblastic anaemia (p. 2109.1) or children with Leber's optic atrophy hydroxocobalamin doses are similar to those used in adults in the UK, see Uses and Administration, above.

Hydroxocobalamin is used as an antidote for cyanide poisoning in children. A dose of 70 mg/kg (maximum 5 g) by intravenous infusion is given once or twice according to severity.

Hydroxocobalamin can also be used in children with methylmalonic acidaemia and homocystinuria, see Amino Acid Metabolic Disorders, below.

Amino acid metabolic disorders. References to the use of hydroxocobalamin in the treatment of inborn errors of vitamin B_{12} metabolism.[1-3] Some patients with homocystinuria (p. 2042.2) or methylmalonic acidaemia have responded to cobalamins—the *BNFC* suggests an initial intramuscular dose of hydroxocobalamin 1 mg daily, for 5 to 7 days, in patients from one month of age; this is reduced, according to response, to 1 mg once or twice weekly. Some children respond to maintenance with 5 to 10 mg hydroxocobalamin given orally once or twice weekly.

1. Linnell JC, Bhatt HR. Inherited errors of cobalamin metabolism and their management. *Baillieres Clin Haematol* 1995; 8: 567–601.
2. Andersson HC, Shapira E. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylmalonic acidemia and homocystinuria (cblC). *J Pediatr* 1998; 132: 121–4.
3. Smith DL, Bodamer OA. Practical management of combined methylmalonicaciduria and homocystinuria. *J Child Neurol* 2002; 17 353–6.

Cardiovascular disease. For mention of the possible link between vitamin B_{12}, hyperhomocysteinaemia, and cardiovascular disease, see under Folic Acid p. 2063.3.

Cyanide toxicity. Hydroxocobalamin combines with cyanide to form cyanocobalamin, and thus may be used as an antidote to cyanide toxicity (see under Hydrocyanic Acid, p. 2156.2). Hydroxocobalamin is reported to be effective in controlling cyanide toxicity due to nitroprusside infusion,[1] and after exposure to inhaled combustion products in residential fires.[2]

It has been hypothesised that the amount of cyanocobalamin formed is limited by the number of cyanide ions present and the amount of hydroxocobalamin given. For a given dose of hydroxocobalamin a maximum concentration of cyanocobalamin would be reached, allowing measurement of cyanocobalamin as a surrogate emergency marker for cyanide levels, which are difficult and time-consuming to measure. For a 5-g dose of hydroxocobalamin given intravenously over 30 minutes, the authors of one study considered a cyanocobalamin concentration of about 300 micromoles/litre a sign that all the hydroxocobalamin had been used, and more should be given.[2] They cautioned, however, that, unless antidote regimen and blood sampling were similar to that in their study, this concentration should not be extrapolated to other patient populations.

In another patient given hydroxocobalamin 5 g intravenously over 2 hours,[3] plasma concentrations of cyanide rose 1 hour after treatment with hydroxocobalamin. The authors attributed this to hydroxocobalamin extracting cyanide from red blood cells to form cyanocobalamin in plasma, which was then measured as cyanide.

A review[4] of the role of hydroxocobalamin in acute cyanide poisoning found insufficient evidence to routinely recommend empirical use for smoke inhalation, although some advantages over standard therapy were noted. Unlike nitrites, hydroxocobalamin does not cause methaemoglobinaemia, a particular risk after smoke inhalation. Additionally, its low toxicity may be beneficial for cyanide toxicity in children and pregnant women.

For doses of hydroxocobalamin used for cyanide toxicity in adults, see Uses and Administration, above, and in children, see Administration in Children, above.

1. Zerbe NF, Wagner BKJ. Use of vitamin B12 in the treatment and prevention of nitroprusside-induced cyanide toxicity. *Crit Care Med* 1993; 21: 465–7.

2. Houeto P, *et al.* Relation of blood cyanide to plasma cyanocobalamin concentration after a fixed dose of hydroxocobalamin in cyanide poisoning. *Lancet* 1995; 346: 605–8.
3. Weng T-I, *et al.* Elevated plasma cyanide after hydroxocobalamin infusion for cyanide poisoning. *Am J Emerg Med* 2004; 22: 492–3.
4. Shepherd G, Velez LI. Role of hydroxocobalamin in acute cyanide poisoning. *Ann Pharmacother* 2008; 42: 661–9.

Deficiency states. The emergence of newer metabolic assays for homocysteine and methylmalonic acid has led to the identification of subtle vitamin B_{12} deficiency[1-3] without the overt manifestations of megaloblastic anaemia (see below) or neurological disease; this condition appears to be particularly common in the elderly.[1,4-6] At present, there is no clear clinical rationale for treating subtle deficiency,[1,7] although suggestions for management have been made.[8] A study in elderly patients suggested that food-cobalamin malabsorption, a disorder characterised by the inability to release vitamin B_{12} from food or its binding protein, might be to blame for this subtle deficiency; these patients had some neurological or haematological abnormalities, and treatment with oral or parenteral vitamin B_{12} was found to be effective.[6] There have also been suggestions that deficiency may be linked to some immunological impairment, identified as impaired antibody responses to pneumococcal vaccine.[9] Moreover, raised homocysteine concentrations have been identified as a risk factor for atherosclerosis and ischaemic heart disease, and there is increasing interest in the potential of B vitamins, including B_{12}, to reduce homocysteine concentrations and therefore atherosclerotic outcomes (see Cardiovascular Disease, under Uses and Administration of Folic Acid, p. 2063.3). Evidence that hyperhomocysteinaemia may be a risk factor for dementia is limited.[5] A systematic review concluded that evidence for efficacy of vitamin B_{12} in improving cognitive function of people with dementia (and low serum vitamin B_{12} concentrations) was lacking.[10]

Dietary vitamin B_{12} deficiency in infants may lead to developmental abnormalities.[11,12]

The issue of fortification of food with folic acid (see under Folic Acid, p. 2064.2) to reduce the number of infants born with neural tube defects (p. 2064.3) has created debate on the risks of masking vitamin B_{12} deficiency, and fortification with vitamin B_{12} has also been recommended, see under Folic Acid, p. 2066.1. An independent association between low maternal vitamin B_{12} status and an increased risk of neural tube defects has also been reported, see Neural Tube Defects, below.

1. Carmel R. Subtle cobalamin deficiency. *Ann Intern Med* 1996; 124: 338–40.
2. Green R. Screening for vitamin B_{12} deficiency: caveat emptor. *Ann Intern Med* 1996; 124: 509–11.
3. Carmel R, *et al.* Update on cobalamin, folate, and homocysteine. *Hematology (Am Soc Hematol Educ Program)* 2003; 62–81.
4. Andrès E, *et al.* Vitamin B_{12}(cobalamin) deficiency in elderly patients. *Can Med Assoc J* 2004; 171: 251–9.
5. Clarke R. Prevention of vitamin B-12 deficiency in old age. *Am J Clin Nutr* 2001; 73: 151–2.
6. Andrès E, *et al.* Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. *Am J Med* 2005; 118: 1154–9.
7. Metz J. What's the use of oral vitamin B_{12}? A neglected but valid treatment route may have new uses in the future. *Med J Aust* 1999; 170: 407.
8. Carmel R. How I treat cobalamin (vitamin B_{12}) deficiency. *Blood* 2008; 112: 2214–21.
9. Fata FT, *et al.* Impaired antibody responses to pneumococcal polysaccharide in elderly patients with low serum vitamin B_{12} levels. *Ann Intern Med* 1996; 124: 299–304.
10. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 09/01/06).
11. Emery ES, *et al.* Vitamin B12 deficiency: a cause of abnormal movements in infants. *Pediatrics* 1997; 99: 255–6.
12. von Schenck U, *et al.* Persistence of neurological damage induced by dietary vitamin B-12 deficiency in infancy. *Arch Dis Child* 1997; 77: 137–9.

Eczema. A small study found that topical application of a preparation containing vitamin B_{12} was more effective than placebo in patients with atopic eczema.[1]

1. Stücker M, *et al.* Topical vitamin B_{12}—a new therapeutic approach in atopic dermatitis—evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. *Br J Dermatol* 2004; 150: 977–83.

Megaloblastic anaemia. The megaloblastic anaemias are characterised by macrocytosis (an increased mean cell volume) and the production of distinctive morphological changes and abnormal maturation in developing haematopoietic cells in the bone marrow: white cell and platelet lines are affected as well as erythroid precursors, and in severe cases anaemia may be associated with leucopenia and thrombocytopenia. Megaloblastic anaemia is a consequence of impaired DNA biosynthesis in the bone marrow, usually due to a deficiency of vitamin B_{12} (cobalamins) or folate, both of which are essential for this process. Although the haematological symptoms of B_{12} deficiency and folate deficiency are similar it is important to distinguish between them since the use of folate alone in B_{12}-deficient megaloblastic anaemia can improve haematological symptoms without preventing aggravation of accompanying neurological symptoms, and may lead to severe nervous system sequelae such as subacute combined degeneration of the spinal cord. Where it is desirable to start therapy immediately, combined treatment for both deficiencies may be started once suitable samples have been taken to permit diagnosis of the deficiency, and the patient converted to the appropriate treatment once the cause of the anaemia is known.

Vitamin B_{12} deficiency anaemia. Vitamin B_{12} deficiency and its associated symptoms may be due to malabsorption (including following gastrectomy), dietary deficiency (mainly in strict vegetarians), competition with intestinal bacteria or parasites, or to the effect of drugs such as nitrous oxide. In populations of northern European origin, pernicious anaemia, in which atrophy of the gastric mucosa results in a lack of the intrinsic factor essential for B_{12} absorption, is the most frequent cause. As body stores of the vitamin are large, it may take several years for signs of deficiency to manifest once the defect in absorption occurs.

In addition to megaloblastic anaemia, vitamin B_{12} deficiency may result in neurological damage, including peripheral neuropathy and effects on mental function ranging from mild neurosis to dementia.

TREATMENT. The treatment is with vitamin B_{12}, almost always by the intramuscular or sometimes the deep subcutaneous route since in most patients absorption from the gastrointestinal tract is inadequate. Hydroxocobalamin is generally preferred to cyanocobalamin since it need be given less often. Regimens may vary, but hydroxocobalamin 1 mg every few days for 6 doses will restore normal body stores of the vitamin (see also Uses and Administration, p. 2108.1). Dosage has not been well established in children; the *BNFC* recommends similar hydroxocobalamin doses to those licensed in adults. The haematological response to therapy is rapid, with improvement in most parameters and symptoms beginning within 48 hours. Neurological abnormalities may take much longer to respond, and may not do so completely.

PROPHYLAXIS. Where the defect in B_{12} handling is irreversible, as in pernicious anaemia, maintenance therapy must continue for life to prevent a recurrence of the deficiency. Therapy must also be given prophylactically after total gastrectomy or total ileal resection, or where gastrointestinal surgery is shown to have impaired absorption of the vitamin. Typically, injection of hydroxocobalamin 1 mg every 3 months is used. In patients whose diet supplies inadequate B_{12}, deficiency may be prevented, in the absence of other causes, by much lower oral doses given as a supplement; up to 150 micrograms of cyanocobalamin daily has been recommended.

Folate-deficiency anaemia. Deficiency of folate may be due to inadequate diet, or malabsorption syndromes (such as coeliac disease or sprue), to increased need (as in pregnancy, one of the most common causes of megaloblastic anaemia, or the increased haematopoiesis of haemolytic syndromes), to increased urinary loss or loss due to haemodialysis, or to an adverse effect of alcohol, antiepileptics, or other drugs.

The clinical features of folate-deficient megaloblastic anaemia are similar to those of disease due to vitamin-B_{12} deficiency except that the accompanying severe neuropathy does not occur, and deficiency may develop much more rapidly. Deficiency may also be associated with neural tube defects (p. 2064.3) if it occurs in pregnancy.

TREATMENT. Once folate deficiency has been established the usual treatment in the UK is oral folic acid 5 mg daily. Lower doses of up to 1 mg are suggested in the USA. It is customary to continue therapy for at least 4 months, the time necessary for complete red cell replacement. In patients with malabsorption, therapy may require higher doses, up to 15 mg of folic acid daily. As in B_{12}-deficiency anaemia, the response to therapy is rapid.

PROPHYLAXIS. Long-term maintenance is rarely needed, except in a few patients in whom the underlying cause of folate deficiency cannot be treated (for example in some severe haemolytic syndromes). Doses of 5 mg daily or even weekly have been suggested for prophylaxis in patients undergoing dialysis or with chronic haemolytic states, depending on the diet and rate of haemolysis; a dose of 400 micrograms daily is recommended in the USA.

For primary prophylaxis of megaloblastic anaemia in pregnancy, folic acid is given in the UK in a usual dose of 500 micrograms daily, often with a ferrous salt for prophylaxis of iron deficiency.

Drugs that act as inhibitors of dihydrofolate reductase, such as methotrexate, may produce severe megaloblastic anaemia which cannot be reversed by therapy with folic acid. The adverse effects of such drugs may be largely prevented or reversed by therapy with folinic acid, which can be incorporated into folate metabolism without the need for reduction by the inhibited enzyme. For details of such 'folinic acid rescue', see under Folinic Acid, p. 2067.1.

General references.

1. Wickramasinghe SN. Folate and vitamin B_{12} deficiency and supplementation. *Prescribers' J* 1997; 37: 88–95.
2. Wickramasinghe SN. The wide spectrum and unresolved issues of megaloblastic anemia. *Semin Hematol* 1999; 36: 3–18.
3. Rasmussen SA, *et al.* Vitamin B_{12} deficiency in children and adolescents. *J Pediatr* 2001; 138: 10–17.
4. Hoffbrand V, Provan D. Macrocytic anaemias. In: Provan D, ed. *ABC of clinical haematology*. 2nd ed. London: BMJ Publishing Group, 2003.
5. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. *Annu Rev Nutr* 2004; 24: 299–326.

Neural tube defects. There is abnormality in homocysteine metabolism in many women who give birth to children with neural tube defects (p. 2064.3); the enzyme methionine synthase, which converts homocysteine to methionine, requires both folate and vitamin B_{12} as cofactors, and low maternal vitamin B_{12} concentrations may be an independent risk factor for neural tube defects.[1] A case-control study found elevated mid-trimester methylmalonic acid concentrations in women with pregnancies affected by neural tube defects, suggesting that abnormalities of cobalamin metabolism, and subsequent methylation, may be involved in the aetiology of neural tube defects.[2] Decreased vitamin B_{12} concentrations, but no folate deficiency, were found in 3 women with pregnancies affected by neural tube defects.[3] A review[4] of case-control studies found a moderate association between low maternal vitamin B_{12} status and the risk of fetal neural tube defects, and results from a Canadian population, largely after folic acid supplementation was implemented, suggested a threefold increase in the risk of neural tube defect in offspring of women with vitamin B_{12} status in the lowest quartile.[5] An Irish study[6] produced similar results. If confirmed by controlled prospective studies, this would suggest that additional supplementation with cobalamins may be warranted.[3-5,7]

1. Mills JL, *et al.* Homocysteine metabolism in pregnancies complicated by neural-tube defects. *Lancet* 1995; 345: 149–51.
2. Adams MJ, *et al.* Elevated midtrimester serum methylmalonic acid levels as a risk factor for neural tube defects. *Teratology* 1995; 51: 311–17.
3. Candito M, *et al.* Anomalies du tube neural et vitamine B12: à propos de trois cas. *Ann Biol Clin (Paris)* 2004; 62: 235–8.
4. Ray JG, Blom HJ. Vitamin B12 insufficiency and the risk of fetal neural tube defects. *Q J Med* 2003; 96: 289–95.
5. Thompson MD, *et al.* Vitamin B-12 and neural tube defects: the Canadian experience. *Am J Clin Nutr* 2009; 89: 697S–701S.
6. Molloy AM, *et al.* Maternal vitamin B_{12} status and risk of neural tube defects in a population with high neural tube defect prevalence and no folic acid fortification. *Pediatrics* 2009; 123: 917–23.
7. Refsum H. Folate, vitamin B12 and homocysteine in relation to birth defects and pregnancy outcome. *Br J Nutr* 2001; 85 (suppl): S109–S113.

Osteoporosis. An elevated serum homocysteine concentration appears to be a risk factor for osteoporotic fractures in older men and women.[1-3] Treatment with vitamin B_{12} and folate can reduce plasma homocysteine concentrations (see Cardiovascular Disease, under Folic Acid, p. 2063.3). In a placebo-controlled study of patients with hemiplegia following stroke (and at increased risk of hip fracture),[4] those given folate and vitamin B_{12} were found to have a significantly reduced risk of hip fracture despite a lack of effect on bone mineral density. Vitamin B_{12} status has been associated with bone health in a number of studies,[3,5] and it was suggested that the observed effects on fracture might be due to increased concentrations of vitamin B_{12} rather than the lowering of plasma homocysteine.[3,6]

1. van Meurs JBJ, *et al.* Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med* 2004; 350: 2033–41.
2. McLean RR, *et al.* Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med* 2004; 350: 2042–9.
3. van Meurs JBJ, Uitterlinden AG. Homocysteine and fracture prevention. *JAMA* 2005; 293: 1121–2.
4. Sato Y, *et al.* Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA* 2005; 293: 1082–8. Correction. *ibid.* 2006; 296: 396.
5. Dhonukshe-Rutten RAM, *et al.* Vitamin B-12 status is associated with bone mineral content and bone mineral density in frail elderly women but not in men. *J Nutr* 2003; 133: 801–7.
6. Sugiyama T, *et al.* Folate and vitamin B_{12} for hip fracture prevention after stroke. *JAMA* 2005; 294: 792.

Rhinitis. A sublingual formulation of cyanocobalamin (*Pre-Histin; Cobalis, USA*) has been reported to be under investigation in the management of seasonal allergic rhinitis, but published studies are lacking.

Adverse Effects and Precautions

Allergic hypersensitivity reactions have occurred rarely after cyanocobalamin and hydroxocobalamin and include skin reactions such as rash and itching, and anaphylaxis. Patients who are hypersensitive to cyanocobalamin injection may be able to take oral cyanocobalamin. Antibodies to hydroxocobalamin-transcobalamin II complex have developed during hydroxocobalamin therapy.

Arrhythmias secondary to hypokalaemia have occurred at the beginning of parenteral treatment with hydroxocobalamin. Injection site reactions including pain, erythema, pruritus, induration, swelling, and necrosis can occur.

Intranasal cyanocobalamin may cause arthralgia, dizziness, headache, nasopharyngitis, and rhinitis; epistaxis has also been reported.

Other adverse effects reported with cyanocobalamin and hydroxocobalamin include gastrointestinal disturbances, fever, chills, hot flushing, dizziness, malaise, acneform and bullous eruptions, and tremor. Headaches, paraesthesia, and chromaturia have occurred with hydroxocobalamin.

Cyanocobalamin or hydroxocobalamin should, if possible, not be given to patients with suspected vitamin B_{12} deficiency without first confirming the diagnosis. Regular monitoring of the blood is advisable. Use of doses greater than 10 micrograms daily may produce a haematological response in patients with folate deficiency; indiscriminate use may mask the precise diagnosis. Conversely, folate may mask vitamin B_{12} deficiency (see p. 2066.1).

Cyanocobalamin should not be used for Leber's disease or tobacco amblyopia since these optic neuropathies may degenerate further.

Breast feeding. Vitamin B_{12} is distributed into breast milk.[1] The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.[2]

1. Samson RR, McClelland DBL. Vitamin B_{12} in human colostrum and milk. *Acta Paediatr Scand* 1980; 69: 93–9.
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 09/01/06)

Hypersensitivity. Analysis, by the Boston Collaborative Drug Surveillance Program, of data on 15 438 patients hospitalised between 1975 and 1982 detected 3 allergic skin reactions attributed to cyanocobalamin among 168 recipients of the drug.[1] For the purposes of the study, reactions were defined as being generalised morbilliform exanthems, urticaria, or generalised pruritus only.

In a patient with a generalised pruritic reaction to hydroxocobalamin (with subsequent urticaria, bronchospasm, and oropharyngeal angioedema), cyanocobalamin was relatively well-tolerated, with only one episode of delayed urticaria.[2]

1. Bigby M, *et al.* Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; 256: 3358–63.
2. Heyworth-Smith D, Hogan PG. Allergy to hydroxycobalamin, with tolerance of cyanocobalamin. *Med J Aust* 2002; 177: 162–3.

Local reactions. After 3 years of monthly intramuscular vitamin B_{12} injections, a patient presented with a sclerotic plaque at the injection site, which was successfully treated by excision and local fat transfer. It was unclear as to whether the patient had reacted to the vehicle, the preservative, or to the cyanocobalamin.[1] Fascial haematoma after vitamin B_{12} injection leading to local compression (posterior arm compartment syndrome) has also been reported.[2]

1. Ho J, *et al.* Vitamin B12-associated localized scleroderma and its treatment. *Dermatol Surg* 2004; 30: 1252–5.
2. Knapke D, Truumees E. Posterior arm and deltoid compartment syndrome after vitamin B12 injection. *Orthopedics* 2004; 27: 520–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyanocobalamin and hydroxocobalamin as not porphyrinogenic: either drug may be used as a drug of first choice and no precautions are needed. Cobamamide and mecobalamin are not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Absorption of vitamin B_{12} from the gastrointestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H_2-antagonists, omeprazole, and colchicine. Serum concentrations may be decreased by use of oral contraceptives. Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations. Parenteral chloramphenicol may attenuate the effect of vitamin B_{12} in anaemia.

Pharmacokinetics

Vitamin B_{12} substances bind to intrinsic factor, a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically. After intranasal dosage, peak plasma concentrations of cyanocobalamin have been reached in 1 to 2 hours. The bioavailability of the intranasal preparation is about 7 to 11% of that by intramuscular injection.

Vitamin B_{12} is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Vitamin B_{12} is stored in the liver, excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Vitamin B_{12} diffuses across the placenta and also appears in breast milk.

Retention in the body. A short review[1] in 1984 noted that after injection of cyanocobalamin a large proportion was excreted in the urine within 24 hours; the body retained only 55% of a 100-microgram dose and 15% of a 1000-microgram dose. Body stores of vitamin B_{12} amounted to 2000 to 3000 micrograms which was believed to be enough for 3 to 4 years. If 1000 micrograms is injected monthly, the 150 micrograms retained lasts for about 1 month. Hydroxocobalamin was better retained than cyanocobalamin; the review stated that 90% of a 100-microgram dose and 30% of a 1000-microgram dose were retained which was believed to be enough for 2 to 10 months. While UK licensed product information supports these figures, it has been pointed out[2] that the latter figure was misquoted by the review from its original source, which claimed that 30% of a 1000 microgram-dose was *excreted* and 70% retained, hence allowing for the longer dosing interval.

1. Anonymous. Time to drop cyanocobalamin? *Drug Ther Bull* 1984; 22: 43.
2. Raymond P. Cyanocobalamin. *Aust Prescriber* 1988; 11: 13.

Human Requirements

For adults, the daily requirement of vitamin B_{12} is probably about 1 to 2 micrograms and this amount is present in most normal diets. Vitamin B_{12} occurs only in animal products; it does not occur in vegetables, therefore strict vegetarian (vegan) diets that exclude dairy products may provide an inadequate amount although it has been said that many years of vegetarianism are necessary before a deficiency is produced, if at all. Meats, especially liver and kidney, milk, eggs, and other dairy products, and fish are good sources of vitamin B_{12}.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p. 2046.1) have been published for vitamin B_{12} and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, adults and pregnant and lactating women. In the UK the reference nutrient intake (RNI) is 1.5 micrograms daily for adult males and females and the estimated average requirement (EAR) is 1.25 micrograms daily. In the USA the RDA for adults is 2.4 micrograms daily.

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 thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Difenac Forte; Lisoneurin B12†; Reedvit; SL B12; Vitam Doce; *Austral.*: Cytamen†; Hydroxo-B12; Neo-B12; Neo-Cytamen†; *Austria*: Cyanokit; Erycytol; Hepavit; *Belg.*: Cyanokit; *Braz.*: Bedozil; Cianon B12†; Cronobe; Enzicoba; Rubranova; *Canad.*: Athlete†; Cyanokit; Formula 1†; Hydro Cobex; Prime†; *China*: Ai Ke Bao (爱柯保); Ai Xin Bao (爱昕保); Bo Di Tong (博迪同); Bo Ke Bao (博可保); Cheng Qiang (成强); Dai Fang (代芳); Fanminbu (泛敏补); He Bao (禾保); Jia Li Bao (加利保); Le Kang (乐亢); LiWei (力维); Luo Tang (洛唐); Methycobal (弥可保); Mi Er Shen (弥尔神); Mi Nuo (弥诺); Ouwei (欧维); Qi Xin (奇信); Qu Li (曲力); Runjie (润洁); Sancoba (散克巴); Shi Er Xin (实尔新); Tang Xin (唐信); Tuo Pu You (托普优); Wei Ke Da (威可达); Yi Shen Bao (怡神保); Yi Wei Kang (怡维康); Yu Hai Xiang (郁海香); Yue Min Xing (悦敏兴); Zhao Min Xin (兆敏欣); *Cz.*: Cyanokit; Neurobene; *Denm.*: Betolvex; Cyanokit; Videden; *Fin.*: Betolvex; Cohemin; *Fr.*: Cyanokit; Dodecavit; Ecovitamine B12; *Ger.*: Ambe 12†; B12 Depot-Rotexmedica; B12 Rotexmedica; B12 Steigerwald; B_{12} Ankermann; B_{12} Depot-Hevert†; B_{12}-ASmedic; Cytobiou†; Lophakomp-B 12 Depot; Lophakomp-B 12; Novirell B_{12}; Rowo Vitamin B_{12} (Rowo-12); *Gr.*: Articlox; Bedoc; *Hong Kong*: Cobalamin†; Cobamin; Cyanokit; Methycobal; Neo-Active Vit B-12†; *Hung.*: Feroglobin-B12; No Shot; *India*: Acmic; Acvit; Adee; Adenomin; Alnacob; Alphamix; Ameco; Amuron; Axineuron; Azed; Balcobal; Basix-OD; Bigvin; Biocobal; Biomic; Cabosoft; Chiny; Citon; Coba; Cobaday; Cobal Forte; Cobal; Cobalom; Cobalvit 1ML; Cobalvit-D; Cobalvit-OD; Cobamet-OD; Cobanerve OD; Cobanerve; Cobaver; Coblona; Cobsa; Compicare; Cubal; Cumee; Diabanerve; Diacobal; E-Cob; Ecobal-OD; Efcoba; Electa; Elmecob; Glomec; Hydrox-12; Ingavit B12; Intacob; Juvinate; Keeneuron; L-Vit-12; Lameco-OD; Logy; Maddox; Malamin; Marinol; Matilda; MB-12; MCB; MCBit; MCBM; Me-12; Mecatin-MD; Mecmin; Mecoba; Mecobal; Mecobest; Mecoflash; Mecofol; Mecolife; Mecomed; Mecona; Meconerv; Meconeuron; Meconovit-OD; Mecophar; Mecoriv; Mecovit; Mecovon; Mecze; Medhamin; Medinerv; Mego; Mellfe-OD; Mericobal; Metherlin; Methico; Methiloc; Methyco; Methycobal; Methygard; Methyneuron; Mewin; Mezen; Mico-B; Miko; Moblo; Mycobal; Mycol; Myconova; Mycotop; Mycovit-OD; Myelogen; Mynuron; Necob; Nervic-1500; Nervicin; Nervon-M; Nervup; Neucobal; Neuractin; Neuratab-M Forte; Neuroage; Neurolac-MD; Neuromed; Neuromin; Neuroswift; Neurotone; Neurotop-M; Neurovig-M; Neutron; Nifabol; Niscobal; Novomine; Nurobex; Nuroclad; Nuroday; Nurokind; Nuromas; Nuromax; Nurovole; Nuroz-OD; Nuthyal Plus; OB-12; Odicoba; Omybal; *Indon.*: Arcored; Berthyco; Cobazim; Ethigobal; Interco; Kalmeco; Lanabal; Lapibal; Magerix; Mecolin; Meconeuro; Megabal; Methycobal; Metifer; Mevrabal†; Nerfeco; Neulamin; Nufacobal; Oxicobal; Scanmecob; Sohobal; *Irl.*: Cyanokit; Cytacon†; Cytamen; Neo-Cytamen; *Israel*: Bedodeka; Bevitex; *Ital.*: Cobaforte; Cyanokit; Dobetin; Indusil; Neo-Cytamen; OH B12; *Jpn*: Methycobal; *Malaysia*: Methycobal; N-Cobal; Neuromethyn; *Mex.*: Axofor; Biocobal†; Biotrefon L; Bissel 12; Compensal†; Duradoce; Exorvit†; Fortical; Leo-Doce†; Maxibol; Nebal; Neurofor; Plusvisol; Sanovit; *Neth.*: Cyanokit; Hydrocobamine; *Norw.*: Betolvex; Cyanokit; *NZ*: Neo-B12; Neo-Cytamen; *Philipp.*: Drexabion; Econvita; Geocobalamin; Heradene; Hybutin; Jaga; Lixtress; Mecovit; Meganerv; Methycobal; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; *Rubramin*†; *Supraneuron; Valcumin; Vineuron; Pol.*: Cyanokit; *Port.*: Co-Vibedoze†; Cobaxid; Cyanokit; Dozefol; Jaba B_{12}; OH B12; Permadoze; *Rus.*: Cicomin (Цикомин); Vitagamma (Витагамма); *S.Afr.*: Cobalatec; *Singapore*: Methycobal; Neuromethyn; *Spain*: Cromatonbic B12; Cyanokit; Isopto B 12; Megamilbedoce; Optovite B12; Reticulogen Fortificado†; Zimadoce†; *Swed.*: Behepan; Behepan; Betolvex; Betolvidon; Cyanokit; *Switz.*: Betolvex; Cyanokit; Vitarubin; *Thail.*: Ampavit; B Twelve P; Balamine; Hitocobamin M†; Mecoba; Mecobal; Mecobin; Mecze; Merabin; Methycobal; Neuromet; Redisol; *Turk.*: Aktibol; Betolvex; Dodex; *UAE*: Cynovit; *UK*: Cobalin-H; Cyanokit; Cytacon; Cytamen; Neo-Cytamen; *USA*: B-12 Dots; B-12 SL; B-12; CaloMist†; Crystamine†; Cyanokit; Cyomin†; Nascobal; Rapid B-12 Energy; Twelve Resin-K; *Venez.*: Bedovit Simple; Beplus; Cristadoce; Dobetin; Hidro-Doce; Ibedox; Maxibol.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. *Ger.*: Hepar comp; Infi-China; Infi-Symphytum; Infihepan; NeyDil Nr 66†; NeyFoc Nr 69; NeyGero Nr 64; NeyGeront Vitalkapsein A; NeyLing Nr 66.

Pharmacopoeial Preparations

BP 2014: Cyanocobalamin Tablets; Hydroxocobalamin Injection; *USP 36*: Cyanocobalamin Injection; Hydroxocobalamin Injection; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; 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; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Vitamin C Substances

Vitamina C; Витамины Группы С

Several substances have vitamin C activity, notably ascorbic acid and its calcium and sodium salts. Natural products with a high vitamin C content include black currant (p. 2458.1), lemon (p. 2542.3), sweet orange (p. 2576.2), and rose fruit (p. 2607.1).

Ascorbic Acid *(BAN, rINN)*

Acide ascorbique; Ácido ascórbico; Acidum Ascorbicum; L-Ascorbic Acid; Ascórbico, ácido; Ascorbinsäure; Askorbiinihappo; Askorbik Asit; Askorbinsyra; Askorbo rūgštis; Aszkorbinsav; Cevitamic Acid; E300; Kwas askorbowy; Kyselina askorbová; Vitamin C; Vitamina C; Аскорбиновая кислота.

The enolic form of 3-oxo-L-gulofuranolactone; 2,3-Didehydro-L-*threo*-hexono-1,4-lactone.

$C_6H_8O_6$=176.1

CAS — 50-81-7.

ATC — A11GA01; G01AD03; S01XA15.

ATC Vet — QA11GA01; QG01AD03; QS01XA15.

UNII — PQ6CK8PD0R.

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

Ph. Eur. 8: (Ascorbic Acid). A white or almost white crystalline powder or colourless crystals becoming discoloured on exposure to air and moisture. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 2.1 to 2.6. Store in nonmetallic containers. Protect from light.

USP 36: (Ascorbic Acid). White or slightly yellow crystals or powder. On exposure to light, it gradually darkens. In the dry state, is reasonably stable in air, but in solution rapidly oxidises. Soluble 1 in 3 of water and 1 in 40 of alcohol; insoluble in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Calcium Ascorbate *(BANM, rINNM)*

Ascorbate de Calcium; Ascorbato cálcico; Askorban vápenatý dihydrát; Calcii Ascorbas; Calcii Ascorbas Dihydricus; Calcium, ascorbate de; Calciumascorbat; E302; Kalcio askorbatas; Kalciumaskorbat; Kalcium-aszkorbát; Kalsiumaskorbaatti; Кальций Аскорбат.

$(C_6H_7O_6)_2Ca,2H_2O=426.3$

CAS — 5743-27-1.

UNII — 183E4W213W (calcium ascorbate dihydrate); J96U0ZD4Y6 (anhydrous calcium ascorbate).

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

Ph. Eur. 8: (Calcium Ascorbate). A white or slightly yellowish crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water has a pH between 6.8 and 7.4. Store in nonmetallic containers. Protect from light.

USP 36: (Calcium Ascorbate). A white to slightly yellow, practically odourless, powder. Freely soluble in water (about 1 in 2); slightly soluble in alcohol; insoluble in ether. pH of a 10% solution in water is between 6.8 and 7.4. Store in airtight containers. Protect from light.

Sodium Ascorbate *(BANM, rINN)*

Ascorbate de sodium; Ascorbate sodique; Ascorbato de sodio; Ascorbato sódico; Askorban sodný; E301; Monosodium L-Ascorbate; Natrii Ascorbas; Natrio askorbatas; Natriumascorbat; Natriumaskorbaatti; Natriumaskorbat; Nátrium-aszkorbát; Натрия Аскорбат.

3-Oxo-L-gulofuranolactone sodium enolate.

$C_6H_7NaO_6=198.1$

CAS — 134-03-2.

UNII — S033EH8359.

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

Ph. Eur. 8: (Sodium Ascorbate). A white or yellowish crystalline powder or crystals. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A freshly prepared 10% solution in water has a pH of 7.0 to 8.0. Store in nonmetallic containers. Protect from light.

USP 36: (Sodium Ascorbate). White or very faintly yellow, odourless or practically odourless, crystals or crystalline powder. On exposure to light it gradually darkens. Soluble 1 in 1.3 of water; very slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 7.0 and 8.0. Store in airtight containers. Protect from light.

Uses and Administration

Vitamin C, a water-soluble vitamin, is essential for the synthesis of collagen and intercellular material. Vitamin C deficiency develops when the dietary intake is inadequate. It is rare in adults, but may occur in infants, alcoholics, or the elderly. Deficiency leads to the development of a well-defined syndrome known as scurvy. This is characterised by capillary fragility, bleeding (especially from small blood vessels and the gums), normocytic or macrocytic anaemia, cartilage and bone lesions, and slow healing of wounds.

Vitamin C is used in the treatment and prevention of deficiency. It completely reverses symptoms of deficiency. It is usually given orally, the preferred route, as ascorbic acid. Ascorbic acid or sodium ascorbate may be given parenterally, preferably by the intramuscular route, but also by the intravenous or subcutaneous routes. Doses of 25 to 75 mg daily in the prevention of deficiency, and 250 mg or more daily in divided doses for the treatment of deficiency, have been recommended.

Oral ascorbic acid 100 to 200 mg daily may be given with desferrioxamine in the treatment of patients with chronic iron overload, to improve the chelating action of desferrioxamine, thereby increasing the excretion of iron (see p. 1544.1); to reduce toxicity ascorbic acid should not be started until 1 month after starting desferrioxamine. Ascorbic acid should be given separately from food since it can enhance iron absorption. In iron deficiency states ascorbic acid is used to increase gastrointestinal iron absorption and ascorbic acid or ascorbate salts are therefore included in some oral iron preparations. Ascorbic acid or sodium ascorbate have been used in treating methaemoglobinaemia. Ascorbic acid has been used to acidify urine. It has also been tried in the treatment of many other disorders (see below) but there is little evidence of beneficial effect.

For doses in children, see Administration in Children, below.

Eye drops containing potassium ascorbate (ascorbic acid 10%) have been used for the treatment of chemical eye burns (p. 1782.1); they may be used with sodium citrate eye drops (see Uses and Administration of Bicarbonate, p. 1781.2).

Ascorbic acid and calcium and sodium ascorbates are used as antioxidants in pharmaceutical manufacturing and in the food industry.

Administration in children. Vitamin C is used in children to prevent and treat deficiency which can lead to scurvy. It is usually given orally as ascorbic acid (although traditional sources for supplementation have included citrus juices, black currant, and rose hip syrup); when the oral route is not feasible or malabsorption is suspected the vitamin may be given parenterally, preferably by the intramuscular route, but also by the intravenous or subcutaneous routes. Doses used for prevention of deficiency are similar to those used in adults, see Uses and Administration, above. In the treatment of scurvy, oral or parenteral doses range from 100 to 300 mg daily, although higher oral doses have also been suggested; the *BNFC* suggests oral doses according to age:

- 1 month to 4 years: 125 to 250 mg daily in 1 or 2 divided doses
- 4 to 12 years: 250 to 500 mg daily in 1 or 2 divided doses
- 12 to 18 years: 500 to 1000 mg daily in 1 or 2 divided doses

Ascorbic acid may also be given with desferrioxamine to increase the excretion of iron; children from 1 month of age may be given the same dose as adults.

Vitamin C may also be given in the treatment of some inherited metabolic disorders such as tyrosinaemia type III, transient tyrosinaemia of the newborn, glutathione synthase deficiency, and Hawkinsinuria. The *BNFC* suggests the following oral doses for specialist use:

- neonate: 50 to 200 mg daily, adjusted as necessary
- 1 month to 18 years: 200 to 400 mg daily in 1 or 2 divided doses, adjusted as necessary; up to 1 g daily may be required

Non-deficiency disorders. A beneficial effect of vitamin C therapy has been claimed for an extraordinary number of conditions, including age-related macular degeneration (under Betacarotene, p. 2051.2) Alzheimer's disease (see Dementia, under Vitamin E, p. 2120.2), atherosclerosis (see Prophylaxis of Ischaemic Heart Disease, p. 2047.1), cancer (see Prophylaxis of Malignant Neoplasms, p. 2047.3), and the common cold (p. 951.1). Other conditions claimed to benefit include asthma, wound healing, psychiatric disorders, infections due to abnormal leucocyte function, infertility, osteogenesis imperfecta, pain in Paget's disease, tetanus, and opioid withdrawal. Generally there are few properly controlled studies to substantiate these claims. Although preliminary evidence suggested a benefit in prevention of pre-eclampsia, this was not confirmed in later studies (see Hypertension, p. 1251.1). Ascorbic acid is also under investigation for the treatment of Charcot-Marie-Tooth syndrome, a chronic and progressive disorder of the nervous system.

Adverse Effects and Precautions

Ascorbic acid is usually well tolerated. Large doses are reported to cause diarrhoea and other gastrointestinal disturbances. It has also been stated that large doses may result in hyperoxaluria and the formation of renal calcium oxalate calculi and ascorbic acid should therefore be given with care to patients with hyperoxaluria (see Effects on the Kidneys, below). Tolerance may be induced with prolonged use of large doses, resulting in symptoms of deficiency when intake is reduced to normal. Prolonged or excessive use of chewable vitamin C preparations may cause erosion of tooth enamel.

Large doses of ascorbic acid have resulted in haemolysis in patients with G6PD deficiency (see Effects on the Blood, below).

Breast feeding. Vitamin C is excreted into breast milk and thus supplied to breast-fed infants. Women in developing countries have significantly lower concentrations of ascorbic acid in their breast milk compared with those in developed countries,[1] and seasonal variation in consumption of foods rich in vitamin C leads to variable amounts of ascorbic acid in breast milk.[2] Supplementation with high-dose ascorbic acid (1 g daily for 10 days) led to significant increases in breast-milk concentrations in both European and African women;[1] however, the overall effect was modest in European women compared with a threefold increase seen in African women. Lower doses of 100 mg daily for 10 days approximately doubled the ascorbic acid breast milk content in the latter, as did supplementation with orange juice 3 or 5 times a week; a significant day-to-day effect was also noted, indicating that the ascorbic acid content of breast milk is regulated. In a small study[2] involving 4 different doses of ascorbic acid supplements, women in West Africa showed that increased intake caused an increase in the ascorbate concentration of breast milk, but concentrations approached a plateau at higher intakes; it was concluded that about 100 to 120 mg of vitamin C daily was needed to achieve acceptable plasma and breast-milk ascorbate concentrations in this population.

1. Daneel-Otterbech S, *et al.* Ascorbic acid supplementation and regular consumption of fresh orange juice increase the ascorbic acid content of human milk: studies in European and African lactating women. *Am J Clin Nutr* 2005; 81: 1088–93.
2. Bates CJ, *et al.* The effect of vitamin C supplementation on lactating women in Keneba, a West African rural community. *Int J Vitam Nutr Res* 1983; 53: 68–76.

Effects on the blood. There are reports of haemolysis in patients with G6PD deficiency after large doses of ascorbic acid either intravenously[1,2] or in soft drinks.[3] There has also been a report[4] of a patient with paroxysmal nocturnal haemoglobinuria suffering haemolysis after taking large amounts of ascorbic acid in a soft drink. There is concern that the large quantities of vitamin C in feeds for premature neonates may have a pro-oxidant effect, and lead to haemolysis. However, a double-blind study found no increase in erythrocyte destruction or hyperbilirubinaemia in premature neonates receiving vitamin C.[5]

1. Campbell GD, *et al.* Ascorbic acid-induced hemolysis in G-6-PD deficiency. *Ann Intern Med* 1975; 82: 810.
2. Rees DC, *et al.* Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency. *BMJ* 1993; 306: 841–2.
3. Mehta JB, *et al.* Ascorbic-acid-induced haemolysis in G-6-PD deficiency. *Lancet* 1990; 336: 944.
4. Iwamoto N, *et al.* Haemolysis induced by ascorbic acid in paroxysmal nocturnal haemoglobinuria. *Lancet* 1994; 343: 357.
5. Doyle J, *et al.* Does vitamin C cause hemolysis in premature newborn infants? Results of a multicenter double-blind, randomized, controlled trial. *J Pediatr* 1997; 130: 103–9.

Effects on the kidneys. Although renal impairment associated with excessive oxalate excretion has been reported with large doses of ascorbic acid[1-3] it has been considered that healthy persons can ingest large amounts of ascorbic acid with relatively small increases in oxalate excretion[4-6] and without an increased risk of oxalate stone formation. A study of vitamin C supplementation with 1 or 2 g given daily for 3 days in calcium stone-forming patients, and 1 g given daily for 3 days in healthy subjects, found that urinary oxalate excretion and the risk of calcium oxalate crystallisation increased significantly in all groups.[7] A prospective cohort study found that increased vitamin C intake (over 1 g daily) was positively associated with the risk of stone formation; an increased risk was observed even at lower intakes of about 90 to 250 mg daily. The risk was raised for both dietary and supplemental vitamin C intake. However, the relation between vitamin C intake and stone formation had emerged only after the inclusion of dietary potassium in the analysis, with potassium intake positively associated with dietary vitamin C intake, but inversely associated with stone formation. This led the authors to conclude that, while limiting dietary vitamin C intake in men with calcium oxalate nephrolithiasis was unwarranted (because of the high potassium content of vitamin C-rich foods), supplemental vitamin C should be avoided.[8]

1. Reznik VM, *et al.* Does high-dose ascorbic acid accelerate renal failure? *N Engl J Med* 1980; 302: 1418–19.
2. Swartz RD, *et al.* Hyperoxaluria and renal insufficiency due to ascorbic acid administration during total parenteral nutrition. *Ann Intern Med* 1984; 100: 530–1.
3. Balcke P, *et al.* Ascorbic acid aggravates secondary hyperoxalemia in patients on chronic hemodialysis. *Ann Intern Med* 1984; 101: 344–5.
4. Tsao CS. Ascorbic acid administration and urinary oxalate. *Ann Intern Med* 1984; 101: 405–6.
5. Wandzilak TR, *et al.* Effect of high dose vitamin C on urinary oxalate levels. *J Urol (Baltimore)* 1994; 151: 834–7.
6. Curhan GC, *et al.* Intake of vitamins B6 and C and the risk of kidney stones in women. *J Am Soc Nephrol* 1999; 10: 840–5.
7. Baxmann AC, *et al.* Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. *Kidney Int* 2003; 63: 1066–71.
8. Taylor EN, *et al.* Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol* 2004; 15: 3225–32.

Effects on mortality. There is some suggestion that serum ascorbic acid concentrations are inversely related to all-cause mortality;[1-4] serum levels were also inversely related to cancer mortality in men but not in women.[1-3] However, a meta-analysis of 3 studies found vitamin C supplementation to have no benefit on mortality in elderly people.[5] A systematic review of antioxidant supplementation in adults also found no significant effect on mortality from studies in which vitamin C was used either singly or with other antoxidants;[6] small beneficial effects or large harmful effects could not be excluded, and since vitamin C can

also act as a pro-oxidant, further studies should monitor closely for any harm.

1. Loria CM, *et al.* Vitamin C status and mortality in US adults. *Am J Clin Nutr* 2000; 72: 139–45.
2. Simon JA, *et al.* Relation of serum ascorbic acid to mortality among US adults. *J Am Coll Nutr* 2001; 20: 255–63.
3. Khaw K-T, *et al.* Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. *Lancet* 2001; 357: 657–63.
4. Fletcher AE, *et al.* Antioxidant vitamins and mortality in older persons: findings from the nutrition add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community. *Am J Clin Nutr* 2003; 78: 999–1010.
5. Ness A, *et al.* Role of antioxidant vitamins in prevention of cardiovascular diseases. *BMJ* 1999; 319: 577.
6. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Effects on the teeth. A report of dental enamel erosion attributed to the daily ingestion of chewable ascorbic acid tablets over a period of 3 years.[1] The tablets lowered the pH of the saliva to a level at which calcium was lost from the tooth enamel.

1. Giunta JL. Dental erosion resulting from chewable vitamin C tablets. *J Am Dent Assoc* 1983; 107: 253–6.

Interference with laboratory tests. Ascorbic acid, a strong reducing agent, interferes with laboratory tests involving oxidation and reduction reactions. Falsely-elevated or false-negative test results may be obtained from plasma, faeces, or urine samples depending on such factors as the dose of ascorbic acid and specific method used.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ascorbic 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 07/10/11)

Interactions

For the effect of ascorbic acid on various drugs see under desferrioxamine (p. 1547.3), hormonal contraceptives (p. 2244.1), HRT (p. 2251.2), fluphenazine (under Chlorpromazine, p. 1053.3), and warfarin (p. 1535.3). Ascorbic acid may increase the absorption of iron in iron-deficiency states. Omeprazole may affect the bioavailability of dietary vitamin C (see Malabsorption, under Omeprazole, p. 1870.2).

Pharmacokinetics

Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Plasma concentrations of ascorbic acid rise as the dose ingested is increased until a plateau is reached with doses of about 90 to 150 mg daily. Body stores of ascorbic acid in health are about 1.5 g although more may be stored at intakes above 200 mg daily. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. In deficiency states the concentration in leucocytes declines later and at a slower rate, and has been considered to be a better criterion for the evaluation of deficiency than the concentration in plasma.

Ascorbic acid is reversibly oxidised to dehydroascorbic acid; some is metabolised to ascorbate-2-sulfate, which is inactive, and oxalic acid which are excreted in the urine. Ascorbic acid in excess of the body's needs is also rapidly eliminated unchanged in the urine; this generally occurs with intakes exceeding 100 mg daily. Ascorbic acid crosses the placenta and is distributed into breast milk. It is removed by haemodialysis.

Human Requirements

A daily dietary intake of about 30 to 100 mg of vitamin C has been recommended for adults. There is, however, wide variation in individual requirements. Humans are unable to form their own ascorbic acid and so a dietary source is necessary. Most dietary ascorbic acid is obtained from fruit and vegetable sources; only small amounts are present in milk and animal tissues. Relatively rich sources include rose hips (rose fruit), black currant, citrus fruits, leafy vegetables, tomatoes, potatoes, and green and red peppers.

Ascorbic acid is readily destroyed during cooking processes. Considerable losses may also occur during storage.

General references.

1. Deruelle F, Baron B. Vitamin C: is supplementation necessary for optimal health? *J Altern Complement Med* 2008; 14: 1291–8.
2. Berger MM. Vitamin C requirements in parenteral nutrition. *Gastroenterology* 2009; 137 (suppl): S70–S78.
3. Lykkesfeldt J, Poulsen HE. Is vitamin C supplementation beneficial? Lessons learned from randomised controlled trials. *Br J Nutr* 2010; 103: 1251–9.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p. 2046.1) have been published for vitamin C and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women. In the UK the reference nutrient intake (RNI) is 40 mg daily for adult males and females and the estimated average requirement (EAR) is 30 mg daily. In general the amount recommended in the USA for all ages and groups is higher than that set in the UK; the RDA is 90 mg daily for men and 75 mg daily for women.[2] The RDA is increased in smokers by 35 mg daily. The tolerable upper intake level is 2 g daily.[2] The EAR is 75 mg daily for men and 60 mg daily for women.

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 vitamin C, vitamin E, selenium, and carotenoids*. Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: C-Vitamin; Cellskinlab Serum 15; Cewin; Citrocola; Citrovita†; Gynefix; Redoxon; Urosedac; Vicenrik; Vita Fizz C; *Austral.*: Cal C; Redoxon†; Sugarless C; VagiCare; *Austria*: Ascorbin; C-Vit; Ce-Limo; Cebion; Cetebe; Cevitol; Iroviton Vitamin C; Mel-C†; *Belg.*: C-Will; Cetamine; Cevi-drops†; Megavitin-C; Redoxon†; Redoxon; Upsa C; *Braz.*: Aceina; Acerogrip C; Active C; Bio-C; Cebion; Ceglen; Cenevit; Cetivit; Cetozone†; Cevita; Cevitonf†; Cewin; Citroplex; Citrovit; Coristina Vitamina C; Energil C; Fonto-Vit C†; Hidracid C20; Hydracid; Redoxon; Vagi C; Vi-Ce; Vitacin; Vitamice; Vitaxon C; Vitergyl C; *Canad.*: Apo-C†; Ascorbplex; Bio-C; C 1000; C 3000†; Ester-C; Formula 1 Bio-C†; Formula 2 Bio-C†; Formula 2†; Inf IC†; Kyolic Formula 103†; Liqui C†; Mega-C; Orti C†; Poly C; Prevegyne; Proflavanol C†; Redoxon; Revitonus C†; Scorbatate†; Super C; Super LSN†; Time Rel Vit C†; UPC†; Vicks Vitamin C Orange; *Chile*: Cebion; Crevet L; Crevet; Esvit C; Mintavit-C; Necta C; Serum 15; Vitac; Vitaseve; *China*: Da Wei Xin (达维欣); Gao Xi (高喜); Jia Xin (嘉欣); Redoxon (力度伸); Upsa C (维善希); Wei Ti Yin (维体因); Xin Wei Xi (新维喜); *Cz.*: Additiva; C-Vitamin; Celaskon; *Denm.*: Bio-C; C-Tabs†; Mega C; Vita Care C-Long†; *Fin.*: Ascorbin†; Bio-C-Vitamin†; C-vimin; Cevi-Tabs†; Poremax-C; *Fr.*: Laroscorbine; Vitascorbol; *Ger.*: Ascorell; Ascorvit; Cebion†; Cetebe; Forum C†; Hermes Cevitt; Macalvit†; Pascorbin; Vagi-C; *Gr.*: Ascorbine; Cebion; Pascorbin; Redoxon; *Icel.* Viforcit; Vitorange; *Hong Kong*: Cecap; Celin†; Cetrinets; Cevit†; Cevizo†; Champs Junior†; Cibion†; Delrosa; Flavettes†; Poten-Cee†; Redoxon†; Vorange; *Hung.*: Beres C; Cebion; Cetebe; Hermes Cevitt; Vitascor†; *India*: Acicon; Aquasol C; Aquasol Ceezed; Bex-C; C-Vit; Cecon; Celin; Cell-C; Frutcee; Immunex; Limcee; Lincee; Sukcee; *Indon.*: Askorbin; Bekamin C; Biferce; Candyvit-C; Cebion†; Ceelin; Champs C; Ever Ce†; Extrace; Fit-C; Flavettes; Sankorbin; Scott's Chewyvit C; Sweeta C; Vicee; Vitacimin; Vitalong C TRC; Vitamex C†; Xon-Ce; Zevit C; *Irl.*: Haliborange Vitamin C; Redoxon†; Rubex; *Israel*: C-Tamin; C500†; Moviprep; Redoxon; *Ital.*: Addivita; Agruvit; Bio-Ci; C Monovit†; C-Tard; Cebion; Cimille; Duo-C†; Dynaphos C; Redoxon; Univit; Vici; *Jpn*: Hicee; *Malaysia*: Ascorbin†; Cecap; Ceelin†; Chewette; Citrex Vitamin C; Upha C; Vita C; *Mex.*: Active C; C-Messel; Ce-Vi-Sol†; Cevalin; Femiprim; Gomas Garde G; Noratoquin; Oxital C; Poly C; Ramy CE; Redoxon; Sinesmin; *Mon.*: Prevegyne; *Neth.*: C-Will; Dayvital; *Norw.*: Bio-C; Nycoplus C-vitamin; *NZ*: Redoxon; *Philipp.*: A-Cee; Alka-C; Asconvita; Ascorbin; Ascorcee; Bonalet-Cee; C-4-Kids; Calcebone; Caldimed; CareZee; Ce-Vi-Sol; Cecon; Cee-protect; Ceelin; Ceenergy; Ceetrus; Cetrasol; Cetrinets; Chewette C; Chilcee; Chilvit-Cee; Citrucin; Cixtor; Clusivol Power C; Day-C-Vit; Daycee; EconoCee; Esviceet; Excel C; EZZ-C; Fern-C; Iconcee; Incee-Vit; Medcee; Myrevit-C; Neo-C; Nutra-Cee; Nutricee; Pedcee; Pediafortan-C; Poten-Cee; Provit-Cee; Supravit-C†; Tropicee; Vamcee; Vi-Cee; Vita-Procee; Zerrucee; *Pol.*: Ascorgem; Ascorvita; Cebion; Cetebe; Cevikap; Juvit; Monovitan C†; Vicefar; Vita-Gem C; *Port.*: Anti-rugas C†; C'Nergil; Cebiolon; Cebion; Cecon†; Cecrisina; Redoxon; Vitaminac Retard; Vivin C†; *Rus.*: Ascovit (Асковит); Celascon (Целаскон); Cetebe (Сетебе); Cevikap (Цевикап); Citravit (Цитравит); Rostvit (Роствит); Upsavit Vitamin C (Упсавит Витамин С); Vaginorm-C (Вагинорм-С); *S.Afr.*: Scorbex; Vitaforce C†; Vitaforce Massif-C†; *Singapore*: Active C; Ascorbin; Biferce; Cebion; Ceelin; Champs C†; Dancimin-C; Flavettes†; Gummi King (Vit C); High-C; Redoxon†; Vorange; *Spain*: Cebion; Citrovit†; Redoxc Redoxon†; *Swed.*: C-vimin; Ido-C; *Switz.*: Cetebe; Demovit C; Redoxon; Vitacen C; *Thai.*: Ascee 500; Bio-C; C Mon; C-Coated; C-Mic; C-Will; CBE; Cibic; Fa-c†; Hicee; MAG-C; Mancevit†; Med-C; Mita-C; Mymin C; Sweetcee; Teddy-C; V-C†; Vio C; Vit C Frx; Vit C-Mile; Vitacee; Vitacimin; Vitamin Cee; Zee; *Turk.*: C-plan; Ester Vit; Hermess Cevit; Monovit-C; Natrol C; Redoxon; Vagi-C; Vitabiol C; *UK*: Buffered C 500; Buffered C; Haliborange Halibonbons; Redoxon; *Ukr.*: Celaskon (Целаскон)†; Cyclo 3 Fort (Цикло 3 Форт); Vaginorm C (Вагинорм С); *USA*: Asco-Caps†; Ascocid; Ascor; Cecon†; Cenolate†; Cevi-Bid†; Chew-C; Dull-C; Halls Defense; N'Ice Vitamin C; Sunkist; Vita-C; *Venez.*: Cebion; Cevax; Cevit; Vitadyn C; Vitrexon.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. *Arg.*: Anemidox Ultra; Anemidox-Ferrum; Anemidox-Solutab; Ferdromaco; Ferro Folic; Ferrocebrina; Hierro Folico; Hierro Plus†; Iberol; Rubiron; Sideralce; Tardyferon; *Austral.*: Bio Iron; FAB; Ferrograd C; Iron Max; *Austria*: Ferretab; Losferron; *Belg.*: Fero-Grad; Losferron; *Braz.*: Cobaldoze†; Combiron; Dobiron; Ferrocomplex; Ferroplex; Iberin Folico; Iberol; Iloban; Novofer; Sulfato Ferroso Composto; *Canad.*: Neo-Fer CP; Palafer CP; *Chile*: Confer Ferranem; Ferranim; Ferro Vitaminico†; Polifer; Iberol Folico†; Iberol†; *Cz.*: Ferro-Folgamma; Losferron†; Sorbifer; Tardyferon-Fol; Tardyferon; *Fin.*: Duroferon; *Fr.*: Bio-Fer†; Fero-Grad vitamine C; Tardyferon B$_9$; Tardyferon; Timoferol *Ger.*: Ferro-Folgamma; Kendural C; Kendural-Fol-500†; Losferron; Tardyferon-Fol; Tardyferon; *Hong Kong*: Iberet-Folic† Iberet†; *Hung.*: Ferro-Folgamma; Floradix; Sorbifer; Tardyferon-Fol; *India*: Alamin-Fez; Anemidox; Autrin; Carnyl-FE Conviron-TR; Hematrine; Hepasules†; Siderfol; *Indon.*: Adfer Bioferron; Bionemi; Biosanbe; Dasabion; Embrion; Emineton Fercee; Feritrin; Ferofort; Habebion†; Hemafort; Hemarate CE†; Hemobion; Iberet-Folic; Iberet; Inbion; Natabion; Neogobion; Nephrovit-Fe; Nichobion; Nonemi; Nufagrabion-GM Nufagrabion; Odiron-C†; Opibion; Ovabion; Prenamia; Prenatin-DP; Sangobion; Sangofer; Sangovitin†; Solvitral; Supra bion; Veroscan; Vica-Natal; Viliron; Vitabion; Vitalex; Vitonal; *Irl.*: Ferrograd C; *Ital.*: Auxofer†; Bioferal; Bioglufer Blustark†; Crom; Cromatonferro; Effegyn; Ergon; Eritropiu Ferro Complex; Ferrograd C; Ferrograd Folic; Ferrogyn Gloros; Losferron; Megafer; Monoferro†; Niferex; Prontoferro Sidervim; *Malaysia*: Iberet-Folic; Opibion; Sangobion; *Mex.* Autrin; Ferro Folico; Fumarol†; Iberet†; Iberol†; *Neth.*: Losferron; *Norw.*: Duroferon; Niferex; *NZ*: Ferrograd C; *Philipp.* Appetite OB; Iberet-Folic; Iberet; Imefer; Macrobee with Iron; Magniferron; Micron-C; Molvite with Iron; Mulvitron Odiron-C†; Sangobion; Sorbifer; Terraferron; TriHEMIC; *Pol.* Additiva Ferrum†; Ascofer; Sorbifer; Tardyferon-Fol; Tardyferon; *Rus.*: Fenules (Фенюлс); Ferro-Folgamma (Феррофольгамма); Ferroplex (Ферроплекс); Gyno-Tardyferon (Гинотардиферон); Hematogen C (Гематоген С); Hematogen C Vit (Гематоген С Вита); Sorbifer (Сорбифер); *S.Afr.*: Autrin† Fero-Folic; Fero-Grad†; Foliglobin; *Singapore*: Iberet-Folic Iberet; Iron Melts; Neogobion; Odiron-C; Opibion; Sangobion; *Swed.*: Duroferon; *Switz.*: Duofer Fol; Duofer; Fero Folic; Ferrascorbin†; Kendural; Lufer†; *Thai.*: Glufer-C† Iberet; Sangobion†; *Turk.*: Ferro-Vital†; Gyno-Tardyferon; Vi Fer; *UK*: Ferrograd C; Floradix; *Ukr.*: Penules (Фенюльс)† Gyno-Tardyferon (Гино-Тардиферон); Sorbifer (Сорбифер) Tardyferon (Тардиферон); *USA*: Chromagen FA; Chromagen Forte; Chromagen†; Contrin; Feocyte; FeoGen; Fero-Folic Fero-Grad; Ferotrinsic; Ferralet 90; Ferrex Forte Plus†; Ferrex Plus; Ferrogels Forte; Fetrin; Fumatinic†; Hem Fe Hematinic Plus; I-L-X; Icar-C Plus; Iron 100 Plus; Irospan Livitrinsic-f†; Multigen; Niferex Forte; Niferex; Pronemi Hematinic; Tandem Plus; TL Icon; Tolfrinic; TriHEMIC; Trimagen†; Trinsicon†; Vitagen Advance; Vitron-C; *Venez.* Fefol; Ferro-Folic; Ferroce B12; Ferroce; Ferronorm; Hepalcon B-12; Iberol C.

Pharmacopoeial Preparations

BP 2014: Ascorbic Acid Injection; Ascorbic Acid Tablets; Chewable Ascorbic Acid Tablets; Paediatric Vitamins A, C and D Oral Drops; Vitamins B and C Injection;

USP 36: Ascorbic Acid Injection; Ascorbic Acid Oral Solution; Ascorbic Acid Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; 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; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets; Zinc and Vitamin C Lozenges.

Vitamin D Substances

Vitamins D; Витамины Группы D.

The term vitamin D is used for a range of closely related sterol compounds including alfacalcidol, calciferdiol, calcitriol, colecalciferol, dihydrotachysterol, and ergocalciferol. Newer vitamin D analogues include doxercalciferol, falecalcitriol, maxacalcitol, and paricalcitol.

Alfacalcidol *(BAN, rINN)*

Alfacalcidolum; Alfakalcidol; Alfakalcidolis; Alfakalsidol; Alfakalsidoli; EB-644; 1-α-Hidroxivitamina D_3; 1α-Hydroxycholecalciferol; 1α-Hydroxyvitamin D_3; 1α-OHD_3; Альфакальцидол.

(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β-diol.

$C_{27}H_{44}O_2$=400.6

CAS — 41294-56-8.

ATC — A11CC03.

ATC Vet — QA11CC03.
UNII — URQ2517572.

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

Ph. Eur. 8: (Alfacalcidol). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Reversible isomerisation to pre-alfacalcidol takes place in solution, depending on temperature and time. Activity is due to both compounds. Store at 2 degrees to 8 degrees under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

Calcifediol *(BAN, USAN, rINN)*

Calcidiol; Calcifédiol; Calcifediolum; Calcifediolum Monohydricum; 25-Hidroxicolecalciferol; 25-Hidroxivitamina D_3; 25-Hydroxycholecalciferol; 25-Hydroxyvitamin D_3; Kalcifediol; Kalcifediol monohydrát; Kalcifediolis; Kalcyfediol; Kalsifediol; 25-(OH)D_3; U-32070E; Кальцифедиол.
(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-3β,25-diol monohydrate.
$C_{27}H_{44}O_2.H_2O$=418.7
CAS — 19356-17-3 (anhydrous calcifediol); 63283-36-3 (calcifediol monohydrate).
ATC — A11CC06.
ATC Vet — QA11CC06.
UNII — P6YZ13C99Q (calcifediol); T0WXW8F54E (anhydrous calcifediol).

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

Ph. Eur. 8: (Calcifediol). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Reversible isomerisation to pre-calcifediol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store at 2 degrees to 8 degrees under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

USP 36: (Calcifediol). Store in airtight containers. Protect from light.

Calcitriol *(BAN, USAN, rINN)*

1α,25(OH)$_2$$D_3$; Calcitriolum; 1α,25-Dihidroxivitamina D_3; 1,25-Dihydroxycholecalciferol; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D_3; Kalcitriol; Kalcitriolis; Kalcytriol; Kalsitriol; Kalsitrioli; Ro-21-5535; Кальцитриол.
(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β,25-triol.
$C_{27}H_{44}O_3$=416.6
CAS — 32222-06-3 (anhydrous); 77326-95-5 (monohydrate).
ATC — A11CC04; D05AX03.
ATC Vet — QA11CC04; QD05AX03.
UNII — FXC9231JVH.

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

Ph. Eur. 8: (Calcitriol). White or almost white crystals. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. It is sensitive to air, heat, and light. A reversible isomerisation to pre-calcitriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store at 2 degrees to 8 degrees under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

USP 36: (Calcitriol). It may be anhydrous or contain one molecule of hydration. White or almost white crystals. Practically insoluble in water; freely soluble in alcohol; soluble in ether and in fatty oils. Store in airtight containers. Protect from light.

Colecalciferol *(BAN, rINN)*

Activated 7-Dehydrocholesterol; Cholécalciférol; Colecalciferol; Colecalciferolum; Colekalciferol; Colekalciferolis; Colekalcyferol; Colécalciférol; Colecalciferolum; Kolekalciferol; Kolekalsiferol; Kolekalsiferoli; Vitamin D_3; Vitamina D_3; Колекальциферол.
(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-trien-3β-ol.
$C_{27}H_{44}O$=384.6
CAS — 67-97-0.
ATC — A11CC05.
ATC Vet — QA11CC05.
UNII — 1C6V77QF41.

Description. Colecalciferol is the naturally occurring form of vitamin D. It is produced from 7-dehydrocholesterol, a sterol present in mammalian skin, by ultraviolet irradiation.

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

Eur. also includes monographs for concentrates in an oily form, a powder form, and a water-dispersible form. *US* also includes a solution.

Ph. Eur. 8: (Colecalciferol; Colecalciferol BP 2014). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in trimethylpentane and in fatty oils. Solutions in solvents without an antioxidant are unstable and should be used immediately. A reversible isomerisation to pre-colecalciferol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store under nitrogen in airtight containers at a temperature of 2 degrees to 8 degrees. The contents of an opened container should be used immediately. Protect from light.

The BP 2014 directs that when calciferol or vitamin D is prescribed or demanded, Colecalciferol or Ergocalciferol shall be dispensed or supplied.

Ph. Eur. 8: (Cholecalciferol Concentrate (Oily Form); Cholecalciferolum Densatum Oleosum; Colecalciferol Concentrate (Oily Form) BP 2014). A solution of colecalciferol in a suitable vegetable oil. It contains not less than 500 000 units/g. It may contain suitable stabilisers such as antoxidants. A clear, yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; miscible with solvents of fats. Partial solidification may occur, depending on the temperature. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of nitrogen.

Ph. Eur. 8: (Cholecalciferol Concentrate (Powder Form); Cholecalciferoli Pulvis; Colecalciferol Concentrate (Powder Form) BP 2014). It is obtained by dispersing an oily solution of colecalciferol in an appropriate matrix which is usually based on a combination of gelatin and carbohydrates of suitable quality. It contains not less than 100 000 units/g. It may contain suitable stabilisers such as antoxidants. White or yellowish-white, small particles. Depending on their formulation, it may be practically insoluble in water or may swell or form a dispersion. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of nitrogen.

Ph. Eur. 8: (Cholecalciferol Concentrate (Water-dispersible Form); Cholecalciferolum in Aqua Dispergibile; Colecalciferol Concentrate (Water-dispersible Form) BP 2014). A solution of colecalciferol in a suitable vegetable oil to which suitable solubilisers have been added. It contains not less than 100 000 units/g. It may contain suitable stabilisers such as antoxidants. A slightly yellowish liquid of variable opalescence and viscosity. Highly concentrated solutions may become cloudy at low temperatures or form a gel at room temperature. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of inert gas.

USP 36: (Cholecalciferol). White, odourless crystals. Insoluble in water; soluble in alcohol, in chloroform, and in fatty oils. M.p. about 85 degrees. It is affected by air and light. Store under nitrogen in hermetically sealed containers at a temperature of 8 degrees to 15 degrees. Protect from light.

USP 36: (Cholecalciferol Solution). A solution of colecalciferol in an edible vegetable oil, in polysorbate 80, or in propylene glycol. Store in airtight containers. Protect from light.

Dihydrotachysterol *(BAN, rINN)*

Dichysterol; Dihidrotakisterol; Dihidrotaquisterol; Dihydrotachystérol; Dihydrotachysterolum; Dihydrotakisterol; Dihydrotakysterol; Dihydrotakysteroli; Дигидротахистерол.
(5*E*,7*E*,22*E*)-10α-9,10-Secoergosta-5,7,22-trien-3β-ol.
$C_{28}H_{46}O$=398.7
CAS — 67-96-9.
ATC — A11CC02.
ATC Vet — QA11CC02.
UNII — R5LM3H112R.

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

Ph. Eur. 8: (Dihydrotachysterol). Colourless crystals, or a white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in *n*-hexane. Store under an inert gas in airtight containers at 2 degrees to 8 degrees.

USP 36: (Dihydrotachysterol). Colourless or white, odourless crystals, or white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform and in ether; sparingly soluble in vegetable oils. Store in hermetic glass containers from which the air has been displaced by an inert gas. Protect from light.

Doxercalciferol *(USAN, rINN)*

Doxercalciférol; Doxercalciferolum; 1α-Hidroxivitamina D_2; 1α-Hydroxyergocalciferol; 1α-Hydroxyvitamin D_2; 1α-OH-D_2; Доксэркальциферол.
(5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraene-1α,3β-diol.
$C_{28}H_{44}O_2$=412.7
CAS — 54573-75-0.
ATC — H05BX03.
ATC Vet — QH05BX03.
UNII — 3DIZ9LF5Y9.

Ergocalciferol *(BAN, rINN)*

Calciferol; Ergocalciférol; Ergocalciferolum; Ergokalciferol; Ergokalciferolis; Ergokalsiferol; Ergokalsiferoli; Irradiated Ergosterol; Viosterol; Vitamin D_2; Vitamina D_2; Эргокальциферол.
(5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraen-3β-ol.
$C_{28}H_{44}O$=396.7
CAS — 50-14-6.
ATC — A11CC01.
ATC Vet — QA11CC01.
UNII — VS041H42XC.

Description. Ergocalciferol is an antirachitic substance obtained from ergosterol, a sterol present in fungi and yeasts, by ultraviolet irradiation.

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

Ph. Eur. 8: (Ergocalciferol). White or almost white, crystals or white or slightly yellowish crystalline powder. It is sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Solutions in volatile solvents are unstable and should be used immediately. A reversible isomerisation to pre-ergocalciferol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store under nitrogen in airtight containers at a temperature of 2 degrees to 8 degrees. The contents of an opened container should be used immediately. Protect from light.

The BP 2014 directs that when calciferol or vitamin D is prescribed or demanded, Ergocalciferol or Colecalciferol shall be dispensed or supplied.

USP 36: (Ergocalciferol). White, odourless crystals. It is affected by air and light. Insoluble in water; soluble in alcohol, in chloroform, in ether, and in fatty oils. Store in hermetically sealed containers under nitrogen at a temperature of 8 degrees to 15 degrees. Protect from light.

Falecalcitriol *(rINN)*

Falécalcitriol; Falecalcitriolum; Flocalcitriol; Hexafluorocalcitriol; Ro-23-4194; ST-630; Фалекальцитриол.
(+)-(5*Z*,7*E*)-26,26,26,27,27,27-Hexafluoro-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol.
$C_{27}H_{38}F_6O_3$=524.6
CAS — 83805-11-2.
UNII — G70A851478.

Maxacalcitol *(USAN, rINN)*

1α,25-Dihydroxy-22-oxavitamin D_3; Maxacalcitolum; OCT; 22-Oxacalcitriol; Sch-209579; Максакальцитол.
(+)-(5*Z*,7*E*,20*S*)-20-(3-Hydroxy-3-methylbutoxy)-9,10-secopregna-5,7,10(19)-triene-1α,3β-diol.
$C_{26}H_{42}O_4$=418.6
CAS — 103909-75-7.
UNII — N2UJM5NBF6.

Paricalcitol *(USAN, rINN)*

ABT-358; Compound 49510; Paracalcin; Paricalcitolum; Парикальцитол.
(7*E*,22*E*)-19-Nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol.
$C_{27}H_{44}O_3$=416.6
CAS — 131918-61-1.
ATC — H05BX02.
ATC Vet — QH05BX02.
UNII — 6702D36OGS.

Pharmacopoeias. In *US.*

USP 36: (Paricalcitol). A white to almost white powder. Insoluble in water; soluble in alcohol. Store under argon in airtight containers at a temperature of -25 degrees to -10 degrees.

Units

The Second International Standard Preparation (1949) of vitamin D consisted of bottles containing about 6 g of a solution of colecalciferol in vegetable oil (1000 units/g). This standard has now been discontinued.

NOTE. Pharmacopoeias consider that one unit of vitamin D is contained in 25 nanograms of colecalciferol or ergocalciferol (i.e. 1 mg of colecalciferol or ergocalciferol is equivalent to 40 000 units of vitamin D as determined by bioassay in *rats*), but see below.

Equivalence. It has been proposed that units of vitamin D be defined in moles or molecules rather than weight terms; in which case, 1 unit of colecalciferol and ergocalciferol would be equivalent to 25 nanograms and 25.78 nanograms, respectively. This inequivalence in units might confound optimal vitamin D dosing recommendations.[1] For the view that colecalciferol is more potent than ergocalciferol, and should be preferred for vitamin D supplementation, see Administration, below.

1. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D_2) as a vitamin supplement. *Am J Clin Nutr* 2006; **84**: 694–7.

Uses and Administration

Vitamin D compounds are fat-soluble sterols, sometimes considered to be hormones or hormone precursors, which are essential for the proper regulation of calcium and phosphate homoeostasis and bone mineralisation.

Vitamin D deficiency develops when there is inadequate exposure to sunlight or a lack of the vitamin in the diet. Deficiency generally takes a long time to develop because of slow release of the vitamin from body stores. It may occur in some infants who are breast fed without supplemental vitamin D or exposure to sunlight, in the elderly whose mobility and thus exposure to light may be impaired, and in persons with fat malabsorption syndromes; certain disease states such as renal failure may also affect the metabolism of vitamin D substances to metabolically active forms and thus result in deficiency.

Deficiency leads to the development of a syndrome characterised by hypocalcaemia, hypophosphataemia, undermineralisation or demineralisation of bone, bone pain, bone fractures, and muscle weakness, known in adults as osteomalacia (see p. 2116.2). In children, in whom there may be growth retardation and skeletal deformity, especially of the long bones, it is known as rickets.

Vitamin D compounds are used in the treatment and prevention of vitamin D deficiency states and hypocalcaemia in disorders such as hypoparathyroidism and secondary hyperparathyroidism, p. 2115.3 and p. 2115.2, respectively.

Many forms and analogues of vitamin D are available, and the choice of agent depends on the cause of the condition to be treated and the relative properties of the available agents. Colecalciferol and ergocalciferol are traditionally considered equal in potency (but see Administration, below), and have a slow onset and relatively prolonged duration of action. Dihydrotachysterol has relatively weak antirachitic activity, but its actions are faster in onset and less persistent than those of the calciferols and it does not require renal hydroxylation. Calcifediol, an intermediate metabolite, has some action of its own but is also converted to the more potent 1,25-dihydroxycholecalciferol (calcitriol); calcitriol and its analogue alfacalcidol are the most potent and rapidly acting of the vitamin D substances.

- For the treatment of simple nutritional deficiencies **colecalciferol** or **ergocalciferol** are generally preferred. They are usually given orally, but may also be given by intramuscular injection. A dose of 10 micrograms (400 units) daily is generally sufficient in adults for the prevention of simple deficiency states; in the UK, 20 micrograms (800 units) daily is recommended in those whose exposure to sunlight is limited, in those whose diet is deficient in vitamin D, and in housebound or institutionalised elderly people. Deficiency due to malabsorption states or liver disease often requires higher doses for treatment, of up to 1 mg (40 000 units) daily. Doses of up to 5 mg (200 000 units) daily may be used in the treatment of hypocalcaemia due to hypoparathyroidism.
- Where large doses are required it may be preferable to use one of the more potent derivatives. In particular, when renal function is impaired as in secondary hyperparathyroidism associated with chronic renal failure, with consequent reduction in the conversion of calciferols to their active metabolites, then a drug such as alfacalcidol, calcitriol, doxercalciferol, maxacalcitol, or paricalcitol, which does not require renal hydroxylation, should be given.

Calcitriol is given orally or by intravenous injection. Usual initial oral doses of 250 nanograms daily or on alternate days are given, increased if necessary, in steps of 250 nanograms at intervals of 2 to 4 weeks, to a usual dose of 0.5 to 1 microgram daily. Initial doses intravenously are usually 500 nanograms three times a week increased if necessary in steps of 250 to 500 nanograms at intervals of 2 to 4 weeks, to a usual dose of 0.5 to 3 micrograms three times a week. For moderate to severe secondary hyperparathyroidism in dialysis patients initial doses of 0.5 to 4 micrograms have been given three times a week, increased if necessary in steps of 250 nanograms to 1 microgram at intervals of 2 to 4 weeks to a maximum of 8 micrograms given three times a week.

Alternatively, **alfacalcidol** is given in initial oral doses of 1 microgram daily, or 500 nanograms for elderly patients. Doses of 0.25 to 1 microgram daily may be given for maintenance. Doses of alfacalcidol may also be given by intravenous injection over 30 seconds.

Doxercalciferol is given orally or by intravenous injection. The initial oral dose is 10 micrograms three times weekly at dialysis, increased by increments of 2.5 micrograms after 8 weeks if necessary. The maximum recommended oral dose is 20 micrograms three times weekly. The initial intravenous dose is 4 micrograms given three times weekly at dialysis, and increased after 8 weeks in increments of 1 to 2 micrograms if required. Doses are titrated according to parathyroid hormone concentrations.

Maxacalcitol is given intravenously at a dose of 2.5 to 10 micrograms three times weekly; the dose may be gradually increased if necessary, to a maximum of 20 micrograms three times weekly.

Paricalcitol is given intravenously in the USA at a dose of 40 to 100 nanograms/kg on alternate days or less frequently; in the UK the initial dose (in micrograms) is calculated by dividing the baseline intact parathyroid hormone concentration (in picograms/mL) by 80. The dose may be increased or decreased if necessary by 2 to 4 micrograms at intervals of 2 to 4 weeks, based on parathyroid hormone concentrations. Paricalcitol is also given orally either as a daily dose or three times weekly (no more frequently than every other day). Again, the initial dose is based on baseline intact parathyroid hormone concentrations. If these are 500 picograms/mL or less, paricalcitol is given at a dose of 1 microgram daily, or 2 micrograms three times weekly; if they are above 500 picograms/mL, paricalcitol 2 micrograms daily, or 4 micrograms three times weekly is suggested. Doses are titrated according to parathyroid hormone concentrations.

- Of the other available forms, **calcifediol**, the 25-hydroxylated metabolite of colecalciferol, may be given in oral doses of up to about 500 micrograms daily for most indications. For hypocalcaemic tetany due to hypoparathyroidism, **dihydrotachysterol** is given in initial oral doses of 750 to 2500 micrograms daily, depending on severity, for about three days. Maintenance doses have ranged from 250 micrograms weekly to 1000 micrograms daily.

When vitamin D substances are given in pharmacological doses, dosage must be individualised for each patient, and should be based on regular monitoring of plasma-calcium concentrations (initially once or twice weekly), to optimise clinical response and avoid hypercalcaemia.

For doses in children, see below and Osteomalacia and Rickets, p. 2116.2.

Vitamin D, usually in the form of calcitriol, may be used in the treatment of osteoporosis (see p. 2116.3). In established postmenopausal osteoporosis, calcitriol 0.25 micrograms twice daily is recommended. Vitamin D and calcium supplements are often given as adjuncts to other therapies in osteoporosis.

Calcitriol has been used in the management of psoriasis (see p. 2117.1); a topical formulation containing maxacalcitol 0.0025% is also available in some countries.

Calciferol derivatives are used as rodenticides.

General references.

1. Thomas MK, Demay MB. Vitamin D deficiency and disorders of vitamin D metabolism. *Endocrinol Metab Clin North Am* 2000; **29**: 611–27.
2. Fuller KE, Casparian JM. Vitamin D: balancing cutaneous and systemic considerations. *South Med J* 2001; **94**: 58–64.
3. Holick MF. Vitamin D: a millenium perspective. *J Cell Biochem* 2003; **88**: 296–307.
4. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr* 2004; **79**: 362–71.
5. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr* 2003; **89**: 552–72.
6. Heaney RP. Vitamin D, nutritional deficiency, and the medical paradigm. *J Clin Endocrinol Metab* 2003; **88**: 5107–8.
7. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* 2004; **80** (suppl): 1678S–1688S.
8. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004; **80** (suppl): 1689S–1696S.
9. Calvo MS, *et al.* Vitamin D intake: a global perspective of current status. *J Nutr* 2005; **135**: 310–16.
10. Bandeira F, *et al.* Vitamin D deficiency: a global perspective. *Arq Bras Endocrinol Metabol* 2006; **50**: 640–6.
11. Mason P. Vitamin D—function and uses. *Pharm J* 2006; **277**: 227–30.
12. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; **357**: 266–81.
13. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008; **87**: 1080S–1086S.
14. Kulie T, *et al.* Vitamin D: an evidence-based review. *J Am Board Fam Med* 2009; **22**: 698–706. Correction. *ibid.* 2010; **23**: 138.
15. Borradale D, Kimlin M. Vitamin D in health and disease: an insight into traditional functions and new roles for the 'sunshine vitamin'. *Nutr Res Rev* 2009; **22**: 118–36.
16. Bischoff-Ferrari H. Vitamin D: what is an adequate vitamin D level and how much supplementation is necessary? *Best Pract Res Clin Rheumatol* 2009; **23**: 789–95.
17. Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010; **340**: b5664.
18. Chesney RW. Vitamin D and the Magic Mountain: the anti-infectious role of the vitamin. *J Pediatr* 2010; **156**: 698–703.

Administration. Minor differences in the chemistry of the side-chains of ergocalciferol and colecalciferol lead to the production of different metabolites (see Pharmacokinetics p. 2118.1).[1] Colecalciferol has been reported to raise serum vitamin D concentrations more effectively than ergocalciferol,[2,3] perhaps because of higher affinities of colecalciferol and its metabolites for liver enzymes, plasma vitamin D binding protein, and vitamin D receptors.[1] It has been suggested that 50 000 units of ergocalciferol should be considered equivalent to no more than 15 000 units of colecalciferol, and perhaps closer to 5000 units; the tolerable upper intake level (see UK and US recommended dietary intake, p. 2118.1) ought not to be applied to ergocalciferol.[3] These differences and the inequivalence in units (see Equivalence, under Units above) may confound optimal vitamin D dosing recommendations.[1,3] The form of vitamin D used in studies should be specified.[2] While ergocalciferol is effective in treating vitamin D deficiency, the differences in potency have led some to suggest that colecalciferol be used as the preferred form of vitamin D.[1,3]

1. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D_2) as a vitamin supplement. *Am J Clin Nutr* 2006; **84**: 694–7.
2. Trang HM, *et al.* Evidence that vitamin D_3 increases serum 25 hydroxyvitamin D more efficiently than does vitamin D_2. *Am J Clin Nutr* 1998; **68**: 854–8.
3. Armas LAG, *et al.* Vitamin D_2 is much less effective than vitamin D_3 in humans. *J Clin Endocrinol Metab* 2004; **89**: 5387–91.

Administration in children. Vitamin D compounds are used to treat deficiency states in children. The *BNFC* suggests initial doses for various indications which should be adjusted thereafter as necessary.

Colecalciferol or **ergocalciferol** can be used to treat nutritional vitamin D deficiency rickets; oral doses vary according to age:

- 1 to 6 months: 75 micrograms (3000 units) daily
- 6 months to 12 years: 150 micrograms (6000 units) daily
- 12 to 18 years: 250 micrograms (10 000 units) daily

Higher initial doses are required in vitamin D deficiency due to intestinal malabsorption or in chronic liver disease, and may be given orally or by intramuscular injection:

- 1 to 12 years: 250 to 625 micrograms (10 000 to 25 000 units) daily
- 12 to 18 years: 250 to 1000 micrograms (10 000 to 40 000 units) daily

Alfacalcidol is used to treat hypophosphataemic rickets, persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism (see also p. 2115.3) in children. Dose may be given orally or by intravenous injection, according to age:

- 1 month to 12 years: 25 to 50 nanograms/kg (maximum 1 microgram) daily
- 12 to 18 years: 1 microgram daily

For persistent neonatal hypocalcaemia, an initial dose of alfacalcidol 50 to 100 nanograms/kg daily may be given orally or by intravenous injection; up to 2 micrograms/kg daily may be needed in resistant cases.

There is less experience with **calcitriol** and it is unlicensed in the UK for use in children, but it may be given for vitamin D dependent rickets, hypophosphataemic rickets, persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism. Doses are given orally according to age:

- 1 month to 12 years: 15 nanograms/kg (maximum 250 nanograms) daily, increased if necessary in steps of 5 nanograms/kg (maximum 250 nanograms) every 2 to 4 weeks
- 12 to 18 years: 250 nanograms daily, increased if necessary in steps of 5 nanograms/kg (maximum 250 nanograms) every 2 to 4 weeks; the usual dose is 0.5 to 1 microgram daily

Hypocalcaemia in dialysis patients may also be treated with calcitriol; intravenous injection of 250 to 500 nanograms (approximately 10 nanograms/kg) may be given three times weekly to children aged 12 to 18 years. This can be increased if needed in steps of 2 to 5 nanograms/kg every 2 to 4 weeks; the usual dose is 0.5 to 3 micrograms three times weekly.

For discussion on doses of vitamin D considered sufficient for prophylaxis of rickets, see UK and US Recommended Dietary Intake, p. 2118.1 and Osteomalacia and Rickets, p. 2116.2. Further discussion on specific disease

states caused by vitamin D deficiency is contained in the abstracts below.

General references on deficiency in children.

1. Misra M, *et al.* Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics* 2008; 122: 398–417.
2. Casey CF, *et al.* Vitamin D supplementation in infants, children, and adolescents. *Am Fam Physician* 2010; 81: 745–8.

Administration in the elderly. Vitamin D deficiency is common in the elderly,[1-3] especially in housebound patients, and during wintertime.[4] Deficiency is aggravated by a diet low in calcium,[1] lack of sunlight exposure, and decreasing ability of the skin to synthesise vitamin D with advancing age.[3,5] Elderly patients are therefore at risk of secondary hyperparathyroidism, bone loss and osteoporosis, and fractures.[1,6,7] Low serum vitamin D has been associated with increased fracture rates, and there is some evidence from *animal* studies that vitamin D may promote bone healing after fracture, increasing the mechanical strength of bone by promoting mineralisation.[7] Poor muscle strength and weakness may be associated with vitamin D deficiency, and may increase the risk of falling in the elderly.[2,8,9] A meta-analysis[10] of 8 controlled studies found that vitamin D supplementation reduced the risk of falls in the elderly by 19% compared with calcium or placebo. Vitamin D deficiency in the elderly may be less prevalent in the USA, due to fortification of food.[1] Food fortification has therefore been recommended,[1] or supplementation with doses in the region of 10 to 20 micrograms (400 to 800 units) daily;[1,4] in the elderly, doses in the region of 17.5 to 25 micrograms (700 to 1000 units) daily are considered necessary for reduction of falls and fractures.[10] The 2005 Dietary Guidelines for Americans recommend that elderly people should consume 25 micrograms (1000 units) daily; the upper level of 50 micrograms (2000 units) should not be exceeded.[5] See also Osteomalacia and Rickets, p. 2116.2 and Osteoporosis, p. 2116.3.

There are also suggestions that low vitamin D concentrations may be associated with various cardiovascular, metabolic, and malignant disorders; for mention of a reduction in total mortality with vitamin D supplementation in mainly elderly people, see UK and US Recommended Dietary Intake, p. 2118.1.

1. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2001; 22: 477–501.
2. Venning G. Recent developments in vitamin D deficiency and muscle weakness among elderly people. *BMJ* 2005; 330: 524–6.
3. Allain TJ, Dhesi J. Hypovitaminosis D in older adults. *Gerontology* 2003; 49: 273–8.
4. Compston JE. Vitamin D deficiency: time for action. *BMJ* 1998; 317: 1466–7.
5. Johnson MA, Kimlin MG. Vitamin D, aging, and the *2005 Dietary Guidelines for Americans*. *Nutr Rev* 2006; 64: 410–21.
6. Passeri G, *et al.* Low vitamin D status, high bone turnover, and bone fractures in centenarians. *J Endocrinol Metab* 2003; 88: 5109–15.
7. Simon J, *et al.* Fractures in the elderly and vitamin D. *J Nutr Health Aging* 2002; 6: 406–12.
8. Moskilde L. Vitamin D and the elderly. *Clin Endocrinol (Oxf)* 2005; 62: 265–81.
9. Janssen HCJP, *et al.* Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr* 2002; 75: 611–15.
10. Bischoff-Ferrari HA, *et al.* Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 2009; 339: b3692. Available at: http://www.bmj.com/cgi/reprint/339/oct01_1/b3692 (accessed 04/02/10)

Cardiovascular disease. Myocardial tissue contains a vitamin D-dependent calcium-binding protein, indicating a role for vitamin D in the regulation of myocardial contractility.[1,2] Lack of vitamin D is considered to play a role in the aetiology and pathogenesis of cardiovascular disease such as congestive heart failure;[2] a case series of 16 infants with cardiomyopathy and heart failure associated with vitamin D deficiency and hypocalcaemia has been reported.[3] Case reports have also shown that vitamin D treatment reduced blood pressure and myocardial hypertrophy.[4] However, systematic reviews of the evidence have come to conflicting conclusions about the value of vitamin D supplementation in preventing cardiovascular events,[5,6] and there is currently no rationale to prescribe specific vitamin D analogues for patients with congestive heart failure.[2]

1. Luong KVQ, Nguyen LTH. Vitamin D and cardiovascular disease. *Curr Med Chem* 2006; 13: 2443–7.
2. Zittermann A, *et al.* Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev* 2006; 11: 25–33.
3. Mutya S, *et al.* Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. *Heart* 2008; 94: 581–4.
4. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol* 2006; 92: 39–48.
5. Pittas AG, *et al.* Systematic review: vitamin D and cardiometabolic outcomes. *Ann Intern Med* 2010; 152: 307–14.
6. Wang L, *et al.* Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 2010; 152: 315–23.

Diabetes mellitus. Vitamin D has a role in glucose homeostasis and in the mechanism of insulin release.[1] Cohort studies[2,3] have suggested that supplementation with vitamin D may have a beneficial role in reducing the risk for developing both type 1 and type 2 diabetes mellitus. A meta-analysis[4] of 5 observational studies also suggested that vitamin D supplementation in early childhood may offer some protection against the development of type I diabetes mellitus. However, another study[5] found no significant differences in vitamin D status in Finnish or Karelian children, 2 neighbouring geographical areas with vastly differing incidences of type 1 diabetes.

Paricalcitol has also been investigated as an adjunct to reduce residual albuminuria in patients with diabetic nephropathy, see p. 465.1.

1. Reis AF, *et al.* Vitamin D endocrine system and the genetic susceptibility to diabetes, obesity and vascular disease: a review of evidence. *Diabetes Metab* 2005; 31: 318–25.
2. Hyppönen E, *et al.* Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001; 358: 1500–1503.
3. Pittas AG, *et al.* Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006; 29: 650–6.
4. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Arch Dis Child* 2008; 93: 512–17.
5. Viskari H, *et al.* Circulating vitamin D concentrations in two neighboring populations with markedly different incidence of type 1 diabetes. *Diabetes Care* 2006; 29: 1458–9.

Hyperparathyroidism. Vitamin D has been used for certain forms of hyperparathyroidism (p. 1170.3). The **secondary hyperparathyroidism** of renal osteodystrophy (p. 1170.1) may respond to treatment with calcitriol, or its analogue alfacalcidol,[1,2] which do not require renal hydroxylation for activation. Calcitriol has been used orally,[3] intravenously,[3,4] and intraperitoneally;[5] percutaneous injection directly into the parathyroid gland has also been reported to be safe and effective.[6-8] However, doses capable of suppressing parathyroid hormone secretion may lead to hypercalcaemia,[1-3,5,9,10] hyperphosphataemia,[1,2,5,9,10] and a decline in renal function;[11] the increase in calcium and phosphate may promote soft tissue and vascular calcification,[1,2] see Hypercalcaemia, under Adverse Effects, p. 2117.2.

Newer analogues for this indication include paricalcitol,[12-15] doxercalciferol,[16-18] falecalcitriol,[19] and maxacalcitol.[20-25] These are reported to have less effect on calcium and phosphate concentrations, while retaining the suppressive effect on parathyroid hormone;[1,5,9,10] however, some[2,18] consider clinically relevant benefit to be lacking. Paricalcitol was found to have a faster effect and cause less hypercalcaemia than calcitriol in patients on haemodialysis,[15] as well as offering a significant survival advantage over calcitriol.[13] A review considered paricalcitol to be as effective and as well tolerated as calcitriol.[14] Maxacalcitol and calcitriol were considered equally effective when given intravenously to haemodialysis patients,[25] while oral falecalcitriol was considered better than oral alfacalcidol at reducing parathyroid hormone concentrations.[19] Intravenous doxercalciferol appears to be safer than oral doxercalciferol;[1] comparative data are lacking.[2,18] A meta-analysis found that the use of vitamin D in chronic kidney disease did not consistently reduce parathyroid hormone concentrations.[26]

Some have cautioned against vitamin D supplementation in **primary hyperparathyroidism** because of concerns about exacerbation of hypercalcaemia and hypercalciuria. However, in a small study in patients with mild primary hyperparathyroidism, correction of vitamin D deficiency did not exacerbate hypercalcaemia, and decreased parathyroid hormone concentrations and bone turnover.[27]

1. Brown AJ, Coyne DW. Vitamin D analogs: new therapeutic agents for secondary hyperparathyroidism. *Treat Endocrinol* 2002; 1: 313–27.
2. Cunningham J. New vitamin D analogues for osteodystrophy in chronic kidney disease. *Pediatr Nephrol* 2004; 19: 705–8.
3. Quarles LD, *et al.* Prospective trial of pulse oral versus intravenous calcitriol treatment of hyperparathyroidism in ESRD. *Kidney Int* 1994; 45: 1710–21.
4. Morosetti M, *et al.* High doses of intravenous calcitriol in the treatment of severe secondary hyperparathyroidism. *J Nephrol* 2004; 17: 95–100.
5. Dusso AS, *et al.* Vitamin D receptor and analogs. *Semin Nephrol* 2004; 24: 10–16.
6. Kitaoka M, *et al.* Percutaneous calcitriol injection therapy (PCIT) for secondary hyperparathyroidism: multicentre trial. *Nephrol Dial Transplant* 2003; 18 (suppl): iii38–iii41.
7. Shiizaki K, *et al.* Effect of percutaneous calcitriol injection therapy on secondary hyperparathyroidism in uraemic patients. *Nephrol Dial Transplant* 2003; 18 (suppl): iii42–iii46.
8. Nakanishi S, *et al.* Efficacy of direct injection of calcitriol into the parathyroid glands in uraemic patients with moderate to severe secondary hyperparathyroidism. *Nephrol Dial Transplant* 2003; 18 (suppl): iii47–iii49.
9. Martín KJ, González EA. Vitamin D analogs: actions and role in the treatment of secondary hyperparathyroidism. *Semin Nephrol* 2004; 24: 456–9.
10. Hudson JQ. Secondary hyperparathyroidism in chronic kidney disease: focus on clinical consequences and vitamin D therapies. *Ann Pharmacother* 2006; 40: 1584–93.
11. Chan JCM, *et al.* A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. *J Pediatr* 1994; 124: 520–8.
12. Martín KJ, *et al.* Therapy of secondary hyperparathyroidism with 19-nor-1α,25-dihydroxyvitamin D_2. *Am J Kidney Dis* 1998; 32 (suppl 2): S61–6.
13. Teng M, *et al.* Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 2003; 349: 446–56.
14. Robinson DM, Scott LJ. Paricalcitol: a review of its use in the management of secondary hyperparathyroidism. *Drugs* 2005; 65: 559–76.
15. Sprague SM, *et al.* Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int* 2003; 63: 1483–90.
16. Frazão JM, *et al.* Intermittent doxercalciferol (1α-hydroxyvitamin D_2) therapy for secondary hyperparathyroidism. *Am J Kidney Dis* 2000; 36: 550–61.
17. Coburn JW, *et al.* Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. *Am J Kidney Dis* 2004; 43: 877–90.
18. Dennis VC, Albertson GL. Doxercalciferol treatment of secondary hyperparathyroidism. *Ann Pharmacother* 2006; 40: 1955–65.
19. Akiba T, *et al.* Controlled trial of falecalcitriol versus alfacalcidol in suppression of parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 1998; 32: 238–46.
20. Akizawa T, *et al.* Long-term effect of 1,25-dihydroxy-22-oxavitamin D (3) on secondary hyperparathyroidism in haemodialysis patients: one-year administration study. *Nephrol Dial Transplant* 2002; 17 (suppl 10): 28–36.
21. Yasuda M, *et al.* Multicenter clinical trial of 22-oxa-1,25-dihydroxyvitamin D3 for chronic dialysis patients. *Am J Kidney Dis* 2003; 41 (suppl 1): S108–S111.
22. Doi S, *et al.* Effect of 22-oxacalcitriol on secondary hyperparathyroidism in hemodialysis patients. *Intern Med* 2003; 42: 955–9.
23. Kubota M, *et al.* The effect of intraperitoneal 22-oxacalcitriol on secondary hyperparathyroidism in continuous ambulatory peritoneal dialysis patients (IPOX Study). *Adv Perit Dial* 2003; 19: 227–30.
24. Murakami K, *et al.* Suppression of parathyroid hormone secretion in CAPD patients by intraperitoneal administration of maxacalcitol. *Clin Exp Nephrol* 2004; 8: 134–8.
25. Hayashi M, *et al.* Comparison of the effects of calcitriol and maxacalcitol on secondary hyperparathyroidism in patients on chronic haemodialysis: a randomized prospective multicentre trial. *Nephrol Dial Transplant* 2004; 19: 2067–73.
26. Palmer SC, *et al.* Meta-analysis: vitamin D compounds in chronic kidney disease. *Ann Intern Med* 2007; 147: 840–53.
27. Grey A, *et al.* Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency. *J Clin Endocrinol Metab* 2005; 90: 2122–6.

Hypoparathyroidism. Although parenteral calcium salts may be given acutely for hypocalcaemic tetany, long-term treatment of hypoparathyroidism (p. 1171.2) usually aims at correction of associated hypocalcaemia with oral calcium salts and oral vitamin D compounds, which increase the intestinal absorption of calcium.

Hypoparathyroidism in *pregnancy* poses severe risks of fetal hyperparathyroidism with neonatal hypocalcaemic rickets, which may be fatal. Treatment with calcium and either colecalciferol or ergocalciferol in doses of 1.25 to 2.5 mg daily, or dihydrotachysterol 0.25 to 1.0 mg daily is essential.[1] Calcitriol, in doses of between 0.25 to 3 micrograms daily, with calcium supplementation, has also been suggested; the dosage is adjusted to physiological requirements during pregnancy.[2]

1. Hague WM. Treatment of endocrine diseases. *BMJ* 1987; 294: 297–300.
2. Callies F, *et al.* Management of hypoparathyroidism during pregnancy - report of twelve cases. *Eur J Endocrinol* 1998; 139: 284–9.

Inflammatory bowel disease. Some studies have found a high prevalence of vitamin D deficiency in patients with inflammatory bowel disease (IBD). The aetiology of this is not entirely clear and may be multifactorial.[1,2] Patients with IBD may have decreased exposure to sunlight since the incidence and prevalence of IBD are greatest in northern latitudes. Patients might also have inadequate dietary intake of vitamin D, since IBD patients may avoid foods, such as dairy products, that are generally fortified with this vitamin. Deficiency might also be due to malabsorption, especially in IBD patients that have undergone small-bowel resection, although intestinal absorption was normal in many IBD patients with low vitamin D concentrations. The use of drugs such as colestyramine, and disturbed enterohepatic circulation of vitamin D metabolites have also been proposed as mechanisms for hypovitaminosis D in patients with IBD, as has an increased loss of vitamin D through protein-losing enteropathy.[1,2] A study[3] in children and young adults with IBD also found a high prevalence of vitamin D deficiency in this patient population. Predisposing factors included dark-skinned complexion, winter season, lack of vitamin D supplementation, early stage of disease, more severe disease, and upper gastrointestinal tract involvement in patients with Crohn's disease. Vitamin D concentrations were positively correlated with serum albumin concentrations, leading the authors to conclude protein-losing enteropathy was a leading mechanism for deficiency. If this were so, both enteral and parenteral supplementation of vitamin D might prove inadequate at the usual dose, and in patients with active disease.

However, the American Gastroenterological Association concluded, in a review of osteoporosis in gastrointestinal diseases,[4] that osteomalacia and vitamin D deficiency were not common in IBD patients (including Crohn's disease) and were unlikely to be causes of most cases of diminished bone mineral density in patients with IBD.

1. Lim W-C, *et al.* Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol* 2005; 2: 308–15.
2. Pappa HM, *et al.* Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. *Inflamm Bowel Dis* 2006; 12: 1162–74.

3. Pappa HM, *et al.* Vitamin D status in children and young adults with inflammatory bowel disease. *Pediatrics* 2006; 118: 1950–61.
4. Bernstein CN, *et al.* American Gastroenterological Association Clinical Practice Committee. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003; 124: 795–841.

Malignant neoplasms. The active form of vitamin D, calcitriol (1,25-dihydroxycholecalciferol) has been found to promote tissue differentiation and to inhibit cellular proliferation *in vitro*. These findings have prompted investigation into the potential role and efficacy of vitamin D metabolites or analogues (sometimes referred to as deltanoids) in malignant neoplasms and in other disorders of cell growth such as psoriasis (see p. 2117.1).

There is laboratory evidence that vitamin D compounds can inhibit the growth of cancer cells, including those of the breast,[1,2] colon,[3] and prostate.[4,5] Epidemiological studies have suggested that vitamin D deficiency may be associated with higher risks of cancer.[6-9] Furthermore, increased sun exposure may be associated with improved survival for some cancers.[7,9] Phase I and II studies of calcitriol either alone, or with antineoplastics, have shown promising results.[10,11] A study in humans has been performed with the calcitriol derivative calcipotriol (p. 1697.2); in this trial calcipotriol used topically in advanced or cutaneous metastatic breast cancer was considered to exert some positive effects and further investigation was considered warranted.[12] Regression of T-cell lymphoma of the skin (mycosis fungoides, p. 698.3) has been reported after application of calcipotriol,[13] and after systemic treatment with calcitriol and a retinoid in a patient who failed to respond to topical calcipotriol.[14] However, 3 other patients with cutaneous T-cell lymphoma failed to respond to calcitriol and isotretinoin,[15] which may have been because of the phenotype or stage of the disease.[16] In a 7-year study in 36 282 postmenopausal women, of whom 18 176 received vitamin D_3(400 units daily) and calcium, supplementation had no effect on the incidence of colorectal cancer.[17] This study has raised debate as to whether the dose of vitamin D used was insufficient.[7] A later analysis[18] of the study results suggested that supplementation had been of benefit in women in the placebo arms of the study but that this had been offset by an increase in risk in women also taking oestrogens. A smaller 4-year study[19] involving 1179 postmenopausal women given calcium with or without vitamin D_3 1100 units daily, or placebo, found that supplementation reduced all-cancer risk, and baseline and treatment-modified serum concentrations of vitamin D were strong predictors of cancer risk.

1. Colston KW, Hansen CM. Mechanisms implicated in the growth regulatory effects of vitamin D in breast cancer. *Endocr Relat Cancer* 2002; 9: 45–59.
2. Cui Y, Rohan TE. Vitamin D, calcium, and breast cancer risk: a review. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 1427–37.
3. Kumagai T, *et al.* Vitamin D_3 analog 19-nor-1,25-dihydroxyvitamin D_3: antitumor activity against leukaemia, myeloma, and colon cancer cells. *J Natl Cancer Inst* 2003; 95: 896–905.
4. Chen TC, Holick MF. Vitamin D and prostate cancer prevention and treatment. *Trends Endocrinol Metab* 2003; 14: 423–30.
5. Stewart LV, Weigel NL. Vitamin D and prostate cancer. *Exp Biol Med (Maywood)* 2004; 229: 277–84.
6. Garland CF, *et al.* The role of vitamin D in cancer prevention. *Am J Public Health* 2006; 96: 252–61.
7. Schwartz GG, Skinner HG. Vitamin D status and cancer: new insights. *Curr Opin Clin Nutr Metab Care* 2007; 10: 6–11.
8. Holick MF. Vitamin D: its role in cancer prevention and treatment. *Prog Biophys Mol Biol* 2006; 92: 49–59.
9. Ingraham BA, *et al.* Molecular basis of the potential of vitamin D to prevent cancer. *Curr Med Res Opin* 2008; 24: 139–49.
10. Trump DL, *et al.* Anti-tumor activity of calcitriol: pre-clinical and clinical studies. *J Steroid Biochem Mol Biol* 2004; 89–90: 519–26.
11. Beer TM, Myrthue A. Calcitriol in cancer treatment: from the lab to the clinic. *Mol Cancer Ther* 2004; 3: 373–81.
12. Bower M, *et al.* Topical calcipotriol treatment in advanced breast cancer. *Lancet* 1991; 337: 701–2. Correction. *ibid.*: 1618.
13. Scott-Mackie P, *et al.* Calcipotriol and regression in T-cell lymphoma of skin. *Lancet* 1993; 342: 172.
14. French LE, *et al.* Remission of cutaneous T-cell lymphoma with combined calcitriol and acitretin. *Lancet* 1994; 344: 686–7.
15. Thomsen K. Cutaneous T-cell lymphoma and calcitriol and isotretinoin treatment. *Lancet* 1995; 345: 1583.
16. French LE, Saurat J-H. Treatment of cutaneous T-cell lymphoma by retinoids and calcitriol. *Lancet* 1995; 346: 376–7.
17. Wactawski-Wende J, *et al.* Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006; 354: 684–96. Correction. *ibid.*; 1102.
18. Ding EL, *et al.* Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women's Health Initiative randomized trial. *Int J Cancer* 2008; 122: 1690–4.
19. Lappe JM, *et al.* Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007; 85: 1586–91. Correction. *ibid.* 2008; 87: 794.

Multiple sclerosis. Multiple sclerosis (p. 996.3) is more common in regions further from the equator, and it has been suggested that sunlight exposure and vitamin D exert a protective effect. Studies have also found lower vitamin D concentrations in patients with multiple sclerosis. Results from two large prospective cohorts found an inverse relationship between intake of vitamin D from supplements and risk of the disease; no association was found between vitamin D intake from food and incidence of multiple sclerosis.[1] A prospective, case-control study[2] found that, among whites, the risk of multiple sclerosis significantly decreased with increasing concentrations of vitamin D; no significant association was found among blacks and Hispanics. However, the sample size in the latter groups were smaller and concentrations of vitamin D are lower among blacks. A review[3] found little evidence to support the effectiveness of vitamin D in the treatment of multiple sclerosis; although uncontrolled studies suggest vitamin D may be beneficial, small patient populations and confounding variables have limited the usefulness of the data.

1. Munger KL, *et al.* Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004; 62: 60–65.
2. Munger KL, *et al.* Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; 296: 2832–8.
3. Brown SJ. The role of vitamin D in multiple sclerosis. *Ann Pharmacother* 2006; 40: 1158–61.

Osteomalacia and rickets. Treatment of osteomalacia and rickets (p. 1168.1) primarily aims at correcting any underlying deficiency states, and vitamin D substances, calcium, or phosphate supplements may be given orally as necessary.

Where rickets is due to impaired synthesis of 1,25-dihydroxycholecalciferol (type I pseudodeficiency) or receptor resistance (type II pseudodeficiency) replacement therapy with calcitriol may be indicated (in the latter case with very high dose calcium),[1] while X-linked hypophosphataemic rickets is generally treated with phosphate supplementation and calcitriol.[2] The use of single large doses of a vitamin D substance (Stosstherapie), for the prophylaxis of rickets, is highly controversial because of problems with toxicity, although it may be effective in patients with rickets due to proven[3] or recalcitrant[4] vitamin D deficiency. Factors contributing to reported resurgences in rickets[2,4-6] include increased breast feeding without sufficient vitamin D supplementation, and less exposure to sunlight. A major risk factor for infants is maternal vitamin D deficiency (see Pregnancy and the Neonate, below). In the UK, the Department of Health advises that children aged 5 years and under be supplemented with 7 micrograms (280 units) daily,[8] but renewed public health campaigns have been called for, along with supplementation of infants from high-risk groups with 400 units of vitamin D daily.[6] Similar recommendations have been made in Australia and New Zealand.[4] Others have commented that even 200 units daily may not be enough as a preventive measure,[2,9] and that, in those children with good exposure to sunlight, calcium supplementation may also be necessary.[10] In 2008, the American Academy of Pediatrics revised its previous advice, increasing the recommended vitamin D intake from a minimum of 200 units daily to 400 units daily for all infants, children, and adolescents beginning in the first few days of life.[11]

In adults, vitamin D deficiency may be asymptomatic. Most patients who present clinically do so because of muscle weakness, or muscles aches and pains.[12] Even severe vitamin D deficiency can go unrecognised; patients may present with a syndrome of persistent, non-specific musculoskeletal pain, before the onset or diagnosis of the clinical presentation of **osteomalacia**.[13,14] Although screening for vitamin D deficiency has been suggested in all patients with this type of musculoskeletal pain,[13] the prevalence of vitamin D deficiency in this patient group has been queried.[15]

For discussion on the intake of vitamin D considered sufficient for prophylaxis, see UK and US Recommended Dietary Intake, p. 2118.1; for treatment in adults, see Uses and Administration, p. 2114.1, and in children, see Administration in Children, p. 2114.3. Because the process of ageing decreases the skin's ability to synthesise vitamin D, elderly people may be at risk of deficiency (see Administration in the Elderly, p. 2115.1).

1. Hochberg Z, *et al.* Calcium therapy for calcitriol-resistant rickets. *J Pediatr* 1992; 121: 803–8.
2. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006; 116: 2062–72.
3. Shah BR, Finberg L. Single-day therapy for nutritional vitamin D-deficiency rickets: a preferred method. *J Pediatr* 1994; 125: 487–90.
4. Munns C, *et al.* Prevention and treatment of infant and childhood vitamin D deficiency in Australia and New Zealand: a consensus statement. *Med J Aust* 2006; 185: 268–72.
5. Kreiter SR, *et al.* Nutritional rickets in African American breast-fed infants. *J Pediatr* 2000; 137: 153–7.
6. Shaw NJ, Pal BR. Vitamin D deficiency in UK Asian families: activating a new concern. *Arch Dis Child* 2002; 86: 147–9.
7. Welch TR, *et al.* Vitamin D-deficient rickets: the reemergence of a once-conquered disease. *J Pediatr* 2000; 137: 143–5.
8. Anonymous. Primary vitamin D deficiency in children. *Drug Ther Bull* 2006; 44: 12–16.
9. Greer FR. Vitamin D deficiency—it's more than rickets. *J Pediatr* 2003; 143: 422–3.
10. Bishop N. Rickets today—children still need milk and sunshine. *N Engl J Med* 1999; 341: 602–4.
11. Wagner CL, Greer FR. American Academy of Pediatrics Section on Breastfeeding. American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008; 122: 1142–52. Correction. *ibid.* 2009; 123: 197.
12. Anonymous. Primary vitamin D deficiency in adults. *Drug Ther Bull* 2006; 44: 25–9.
13. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D i patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Pr* 2003; 78: 1463–70.
14. Sievenpiper JL, *et al.* Unrecognised severe vitamin D deficiency. *BM* 2008; 336: 1371–4.
15. Block SR. Vitamin D deficiency is not associated with nonspecifi musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Pr* 2004; 79: 1585–6.

PREGNANCY AND THE NEONATE. It has been supposed tha most infants receive adequate calcium and vitamin D dur ing pregnancy and during breast feeding or bottle feedin to prevent the development of rickets. However, this ha been disputed;[1,2] even infants born to vitamin D replet mothers become vitamin D deficient after 8 weeks if no supplemented, and those born to vitamin D deficien mothers will reach a deficient state more quickly. In many populations where sun exposure is severely limited an there is inadequate corrective vitamin D supplementation there is also a high prevalence of vitamin D deficiency ir nursing mothers.[3] It is accepted that there are certain groups of women whose infants may be at special risk o neonatal rickets; these include those suffering economi deprivation, those living at high latitudes, and Asian immigrants [i.e. from the Indian subcontinent] in north ern Europe, especially in winter. It is therefore suggested that pregnant women in such circumstances should receive supplements as the diet and sunshine exposure may not be providing adequate calcium (1 to 1.2 g daily or vitamin D (400 units daily).[4] Alternatively, 1000 units vitamin D daily during the third trimester, or a single dose of 100 000 to 200 000 units of ergocalciferol during the sixth or seventh month, has been proposed.[5] The Committee on Medical Aspects of Food Policy (COMA) in the UK recommended[6] in 1991 that pregnant women receive supplementary vitamin D to achieve an intake of 10 micrograms daily. A 2008 report[7] commissioned by NICE recommended that women should be informed about the importance, for their own and their baby's health, o maintaining adequate vitamin D stores during pregnancy and while breastfeeding and stated that in order to achieve this, women may choose to take 10 micrograms of vitamin D daily. However, the report also stated that while there is some evidence of benefit from vitamin D supplementation for pregnant women at risk of vitamin D deficiency, there is less evidence in the case of those currently regarded as being at low risk of deficiency. A review[2] of dietary vitamin D requirements during pregnancy and lactation has stated that women who were vitamin D deficient at the beginning of their pregnancy remained deficient despite supplementation with 800 to 1600 units daily. The authors suggested that current recommendations in the UK and the USA were grossly inadequate during pregnancy, especially for ethnic minorities (see UK and US recommended dietary intake, p. 2118.1). Instead, they suggested that doses of about 2000 to 10 000 units daily would be needed in order to achieve normal vitamin D concentrations. Furthermore, routine vitamin D supplementation of infants in high-risk groups has been recommended (see Osteomalacia and Rickets, above).

1. Welch TR, *et al.* Vitamin D-deficient rickets: the reemergence of a once-conquered disease. *J Pediatr* 2000; 137: 143–5.
2. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr* 2004; 79: 717–26.
3. Dawodu A, Wagner CL. Mother-child vitamin D deficiency: an international perspective. *Arch Dis Child* 2007; 92: 737–40.
4. Misra R, Anderson DC. Providing the fetus with calcium. *BMJ* 1990; 300: 1220–1.
5. Shaw NJ, Pal BR. Vitamin D deficiency in UK Asian families: activating a new concern. *Arch Dis Child* 2002; 86: 147–9.
6. 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.
7. 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/live/11947/40145/40145.pdf (accessed 22/07/10)

Osteopetrosis. For mention of the use of high-dose calcitriol in the management of osteopetrosis, see under Corticosteroids, p. 1609.3.

Osteoporosis. Vitamin D concentrations have been found to correlate positively with bone mineral density (BMD),[1] and supplementation with vitamin D and calcium has led to beneficial increases in BMD in most trials.[2] Sufficient intake of vitamin D and calcium is recommended for prevention of osteoporosis (p. 1168.1), and supplementation is an accepted baseline adjunctive treatment.[2,3] The age-related increase in fracture risk is influenced by BMD changes and an increased propensity to falls, attributable in part to a loss of muscular strength. In addition to its role in calcium homoeostasis, vitamin D status has also been correlated to muscular strength in older people.[3]

Studies using vitamin D (with or without calcium) for the prevention of fractures have produced conflicting results.[4-11] However, in elderly patients, in whom dietary deficiencies are common, calcium and vitamin D supplements are recommended (see Administration in the Elderly, p. 2115.1). Supplementation is also recommended in elderly

institutionalised patients.[12] A meta-analysis[13] of fracture prevention studies found that oral vitamin D supplementation with between 700 to 800 units daily reduced the risk of hip and non-vertebral fractures in elderly patients. However, a systematic review[11] has stated that vitamin D alone is unlikely to prevent fractures.

Calcium may be necessary to optimise the clinical efficacy of vitamin D supplementation in terms of reducing fracture risk.[3] A meta-analysis[14] found that oral vitamin D appeared to reduce the risk of hip fractures only when calcium supplementation was added. However, another meta-analysis[15] found that the difference in relative risk reduction for all fracture types when vitamin D was added to calcium supplementation, was very small and statistically insignificant, although those with low vitamin D serum concentrations tended to have a greater risk reduction than those with normal vitamin D concentrations. A significant difference was seen between the effects of different vitamin D doses. While noting that this could be due to statistical artifact, the authors noted that their analysis had been limited by the scarcity of data for vitamin D doses higher than 800 units, and that it was possible that vitamin D would have a beneficial effect if the dose were greater than 800 units daily.

It has been suggested[16] that the vitamin D analogues alfacalcidol and calcitriol are more effective for osteoporosis than ergocalciferol or colecalciferol. However, a systematic review[11] found no evidence of benefit for analogues compared with vitamin D. Another systematic review[17] found that vitamin D supplementation overall reduced falls and nonvertebral but not vertebral fractures; however, subgroup analysis suggested a reduction in vertebral fractures with alfacalcidol but not with calcitriol.

Vitamin D is also recommended for the prevention of corticosteroid-induced osteoporosis (see Effects on Bones and Joints, p. 1616.2).

1. Bischoff-Ferrari HA, *et al.* Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med* 2004; 116: 634–9.
2. Rodríguez-Martínez MA, García-Cohen EC. Role of Ca^{2+} and vitamin D in the prevention and treatment of osteoporosis. *Pharmacol Ther* 2002; 93: 37–49.
3. Boonen S, *et al.* Calcium and vitamin D in the prevention and treatment of osteoporosis—a clinical update. *J Intern Med* 2006; 259: 539–52.
4. Lips P, *et al.* Vitamin D supplementation and fracture incidence in elderly persons. *Ann Intern Med* 1996; 124: 400–6.
5. Dawson-Hughes B, *et al.* Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997; 337: 670–6.
6. Trivedi DP, *et al.* Effect of four monthly oral vitamin D_3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003; 326: 469.
7. Porthouse J, *et al.* Randomised controlled trial of supplementation with calcium and cholecalciferol (vitamin D_3) for prevention of fractures in primary care. *BMJ* 2005; 330: 1003–6.
8. The RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 2005; 365: 1621–28.
9. Jackson RD, *et al.* Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; 354: 669–83. Correction. *Ibid.*: 1102.
10. Dhesi JK, *et al.* The implications of a growing evidence base for drug use in elderly patients: Part 4: Vitamin D and bisphosphonates for fractures and osteoporosis. *Br J Clin Pharmacol* 2006; 61: 521–8.
11. Avenell A, *et al.* Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 22/07/10).
12. Anonymous. Lifestyle advice for fracture prevention. *Drug Ther Bull* 2002; 40: 83–6.
13. Bischoff-Ferrari HA, *et al.* Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 2005; 293: 2257–64.
14. Boonen S, *et al.* Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. *J Clin Endocrinol Metab* 2007; 92: 1415–23.
15. Tang BMP, *et al.* Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007; 370: 657–66.
16. Ringe JD, Schacht E. Prevention and therapy of osteoporosis: the roles of plain vitamin D and alfacalcidol. *Rheumatol Int* 2004; 24: 189–97.
17. O'Donnell S, *et al.* Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. *J Bone Miner Metab* 2008; 26: 531–42.

Psoriasis. A vitamin D analogue, calcipotriol (p. 1697.2), is often used as an alternative to more traditional topical drugs in the initial management of mild to moderate psoriasis (p. 1688.1). Another vitamin D analogue, tacalcitol (p. 1722.1), is used similarly. Initial studies with topical maxacalcitol,[1] falecalcitriol,[2] and paricalcitol[3] suggest they are safe and effective for psoriasis. Calcitriol itself has been tried, both topically[4-6] and orally.[7] Calcitriol ointment has been found to be as effective as calcipotriol ointment[8] and short-contact dithranol cream; skin irritation was less with calcitriol compared with dithranol.[9] While global improvement and severity scores were found to be better with betamethasone dipropionate ointment, remission times were longer with calcitriol treatment.[10]

1. Barker JNWN, *et al.* Topical maxacalcitol for the treatment of psoriasis vulgaris: a placebo-controlled, double-blind, dose-finding study with active comparator. *Br J Dermatol* 1999; 141: 274–8.
2. Durakovic C, *et al.* Rationale for use and clinical responsiveness of hexafluoro-1,25-dihydroxyvitamin D_3 for the treatment of plaque psoriasis: a pilot study. *Br J Dermatol* 2001; 144: 500–506.
3. Durakovic C, *et al.* Topical paricalcitol (19-nor-1 α ,25-dihydroxyvitamin D_2) is a novel, safe and effective treatment for plaque psoriasis: a pilot study. *Br J Dermatol* 2004; 151: 190–5.
4. Sips AJAM, *et al.* Topically applied low-dose calcitriol has no calciotropic effect in patients with stable plaque psoriasis. *J Am Acad Dermatol* 1994; 30: 966–9.
5. Langner A, *et al.* A long-term multicentre assessment of the safety and tolerability of calcitriol ointment in the treatment of chronic plaque psoriasis. *Br J Dermatol* 1996; 135: 385–9.
6. Ring J, *et al.* Calcitriol 3 micrograms g^{-1} ointment in combination with ultraviolet B phototherapy for the treatment of plaque psoriasis: results of a comparative study. *Br J Dermatol* 2001; 144: 495–9.
7. Perez A, *et al.* Safety and efficacy of oral calcitriol (1,25-dihydroxyvitamin D_3) for the treatment of psoriasis. *Br J Dermatol* 1996; 134: 1070–8.
8. Lahfa M, *et al.* Calcitriol ointment and clobetasol propionate cream: a new regimen for the treatment of plaque psoriasis. *Eur J Dermatol* 2003; 13: 261–5.
9. Hutchinson PE, *et al.* The efficacy, safety and tolerance of calcitriol 3 micrograms/g ointment in the treatment of plaque psoriasis: a comparison with short-contact dithranol. *Dermatology* 2000; 201: 139–45.
10. Camarasa JM, *et al.* Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. *J Dermatol Treat* 2003; 14: 8–13.

Renal osteodystrophy. See under Hyperparathyroidism, p. 2115.2.

Rheumatoid arthritis. A large cohort study[1] found an inverse correlation between vitamin D intake and the risk of developing rheumatoid arthritis. However, a small study[2] of serum vitamin D concentrations in patients with rheumatoid arthritis who had donated blood before the onset of symptoms, found no association between vitamin D deficiency and later development of rheumatoid arthritis, suggesting that vitamin D does not have an important role in the pathogenesis of rheumatoid arthritis.

1. Merlino LA, *et al.* Vitamin D intake is inversely associated with rheumatoid arthritis. *Arthritis Rheum* 2004; 50: 72–7.
2. Nielen MMJ, *et al.* Vitamin D deficiency does not increase the risk of rheumatoid arthritis: comment on the article by Merlino et al. *Arthritis Rheum* 2006; 54: 3719–20.

Rickets. See Osteomalacia and Rickets, p. 2116.2.

Adverse Effects and Treatment

Excessive intake of vitamin D leads to the development of hyperphosphataemia or hypercalcaemia. Associated effects of hypercalcaemia include hypercalciuria, ectopic calcification, and renal and cardiovascular damage (for a discussion of vitamin-D mediated hypercalcaemia and its treatment, see p. 1776.1). Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence, and vertigo. Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin should be withdrawn if toxicity occurs. It has been stated that vitamin D dietary supplementation may be detrimental in persons already receiving an adequate intake through diet and exposure to sunlight, since the difference between therapeutic and toxic concentrations is relatively small.

The most potent forms of vitamin D, such as alfacalcidol and calcitriol, might reasonably be expected to pose a greater risk of toxicity; however, their effects are reversed rapidly on withdrawal.

Hypersensitivity reactions have occurred. Skin irritation or contact dermatitis has been reported with topical preparations.

Hypercalcaemia. Vitamin D is the most likely of all vitamins to cause overt toxicity. Doses of 60 000 units daily can cause hypercalcaemia (p. 1776.1), with muscle weakness, apathy, headache, anorexia, nausea and vomiting, bone pain, ectopic calcification, proteinuria, hypertension, and cardiac arrhythmias. Chronic hypercalcaemia can lead to generalised vascular calcification, nephrocalcinosis, and rapid deterioration of renal function.[1,2] A number of reports of accidental overdosage, leading to hypercalcaemia or nephrocalcinosis, occurred in the UK after introduction of a concentrated alfacalcidol oral solution that was 10 times stronger than the former presentation.[3]

Hypercalcaemia has been reported in a patient after brief industrial exposure to colecalciferol.[4]

A study in children treated for renal osteodystrophy has provided some evidence that hypercalcaemia may occur more frequently with calcitriol than with ergocalciferol.[5] Another such study has suggested that vitamin D has nephrotoxic properties independent of the degree of induced hypercalcaemia, and that the decline in renal function may be more marked with calcitriol.[6]

Topical calcitriol may affect calcium homoeostasis, and hypercalcaemia has been reported in some studies.[7] For reference to the effect of other vitamin D analogues used in psoriasis on calcium homoeostasis, see under Calcipotriol, p. 1698.2.

1. Anonymous. Toxic effects of vitamin overdosage. *Med Lett Drugs Ther* 1984; 26: 73–4.
2. Chiticone D, *et al.* Unusual cases of chronic intoxication by vitamin D. *J Nephrol* 2003; 16: 917–21.
3. CSM/MCA. Accidental overdose with alfacalcidol (One-Alpha drops). *Current Problems* 2001; 27: 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 09/01/06)
4. Jibani M, Hodges NH. Prolonged hypercalcaemia after industrial exposure to vitamin D_3. *BMJ* 1985; 290: 748–9.
5. Hodson EM, *et al.* Treatment of childhood renal osteodystrophy with calcitriol or ergocalciferol. *Clin Nephrol* 1985; 24: 192–200.
6. Chan JCM, *et al.* A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. *J Pediatr* 1994; 124: 520–8.
7. Bourke JP, *et al.* Vitamin D analogues in psoriasis: effects on systemic calcium homeostasis. *Br J Dermatol* 1996; 135: 347–54.

Precautions

Vitamin D should not be given to patients with hypercalcaemia. It should be used with caution in infants, who may have increased sensitivity to its effects, and patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcaemia occurred. Plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification.

It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially or if symptoms suggest toxicity (see above). Similar monitoring is recommended in infants if they are breast-fed by mothers receiving pharmacological doses of vitamin D (see below).

Breast feeding. Vitamin D is distributed into breast milk,[1] and its concentration appears to correlate with the amount of vitamin D in the serum of exclusively breast-fed infants.[2] The American Academy of Pediatrics considers the use of vitamin D to be usually compatible with breast feeding,[3] although they and others[4] recommend that the infant be closely monitored for hypercalcaemia or clinical manifestations of vitamin D toxicity if the mother is taking pharmacological doses of vitamin D.

1. Rothberg AD, *et al.* Maternal-infant vitamin D relationships during breast-feeding. *J Pediatr* 1982; 101: 500–503.
2. Cancela L, *et al.* Relationship between the vitamin D content of maternal milk and the vitamin D status of nursing women and breast-fed infants. *J Endocrinol* 1986; 110: 43–50.
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 09/01/06)
4. Greer FR, *et al.* High concentrations of vitamin D_2 in human milk associated with pharmacologic doses of vitamin D_2. *J Pediatr* 1984; 109: 61–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alfacalcidol, calcitriol, colecalciferol, and dihydrotachysterol as probably not porphyrinogenic; these may be used as drugs of first choice and no precautions are needed. Calcifediol, ergocalciferol, and paricalcitol are not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy. Indeed, one report noted increased requirements for vitamin D preparations during pregnancy for the treatment of hypoparathyroidism;[1] the dose needed tended to increase during the second half of pregnancy. In one woman in whom the dose of calcitriol remained raised after delivery (in an attempt to allow for the calcium loss involved in breast feeding) hypercalcaemia developed; this did not occur in 2 women who did not breast feed and in whom the dose of the vitamin D preparations was reduced soon after delivery.[1] For discussions regarding vitamin D requirements during pregnancy, see UK and US recommended dietary intake, p. 2118.1, and Pregnancy and the Neonate, p. 2116.3.

1. Caplan RH, Beguin EA. Hypercalcemia in a calcitriol-treated hypoparathyroid woman during lactation. *Obstet Gynecol* 1990; 76: 485–9.

Interactions

There is an increased risk of hypercalcaemia if vitamin D is given with thiazide diuretics, calcium, or phosphate. Plasma-calcium concentrations should be monitored in such situations. Some antiepileptics may increase vitamin D requirements (e.g. carbamazepine, phenobarbital, phenytoin, and primidone). Rifampicin and isoniazid may reduce

the effectiveness of vitamin D. Corticosteroids may counteract the effect of vitamin D. Ketoconazole may inhibit the metabolism of paricalcitol and these drugs should be used with caution together; care should be taken when using paricalcitol with other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4.

Danazol. A report of hypercalcaemia associated with danazol in a patient maintained on alfacalcidol therapy for hypoparathyroidism.[1] Introduction of danazol appeared to reduce the maintenance requirement for alfacalcidol.

1. Hepburn NC, *et al.* Danazol-induced hypercalcaemia in alphacalcidol-treated hypoparathyroidism. *Postgrad Med J* 1989; 65: 849–50.

Levothyroxine. Three patients taking dihydrotachysterol and calcium, for postoperative hypoparathyroidism after thyroidectomy, as well as levothyroxine, developed hypercalcaemia when the latter was stopped before a radio-iodine scan.[1] The dose of dihydrotachysterol should be reduced and serum-calcium concentrations should be monitored when thyroid treatment is interrupted, since elimination of dihydrotachysterol may be delayed in hypothyroidism.

1. Lamberg B-A, Tikkanen MJ. Hypercalcaemia due to dihydrotachysterol treatment in patients with hypothyroidism after thyroidectomy. *BMJ* 1981; 283: 461–2.

Pharmacokinetics

Vitamin D substances are well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption; absorption may be decreased in patients with decreased fat absorption.

Vitamin D and its metabolites circulate in the blood bound to a specific α-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Ergocalciferol and colecalciferol have a slow onset and a long duration of action; calcitriol and its analogue alfacalcidol, however, have a more rapid action and shorter half-lives.

Colecalciferol and ergocalciferol are hydroxylated in the liver by the enzyme vitamin D 25-hydroxylase to form 25-hydroxycholecalciferol (calcifediol) and 25-hydroxyergocalciferol respectively. These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D 1-hydroxylase to form the active metabolites 1,25-dihydroxycholecalciferol (calcitriol) and 1,25-dihydroxyergocalciferol respectively. Further metabolism also occurs in the kidneys, including the formation of the 1,24,25-trihydroxy derivatives. Of the synthetic analogues, alfacalcidol, dihydrotachysterol, and doxercalciferol are converted directly in the liver to their active metabolites (calcitriol, 25-hydroxydihydrotachysterol, and 1,25-dihydroxyergocalciferol respectively).

Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

Human Requirements

The daily requirements of vitamin D in adults are small and may be met mainly by exposure to sunlight and/or obtained from the diet. A daily dietary intake of about 200 to 400 units (5 to 10 micrograms of colecalciferol or ergocalciferol) of vitamin D is generally considered adequate for healthy adults. In comparison with older adults (in the age range of 25 years upwards) the requirements per kg bodyweight are greater in infants, children, and young adults and during pregnancy and lactation. Requirements may also be higher in people who are not exposed to adequate sunlight such as the elderly or housebound.

Vitamin D is present in few foods. Fish-liver oils, especially cod-liver oil, are good sources of vitamin D. Other sources, which contain much smaller amounts, include butter, eggs, and liver. Some foods are fortified with vitamin D, and milk and margarine may therefore also supply the vitamin. Cooking processes do not appear to affect the activity of vitamin D.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) for vitamin D have only been published for selected groups of the population.[1] In the USA recommended dietary allowances had been set, and were subsequently replaced by dietary reference intakes[2] (see p. 2046.1). Differing amounts are recommended for infants and children of varying ages, for adults, and for pregnant and lactating women. In the UK a dietary intake was considered unnecessary for adults living a normal lifestyle who were being exposed to solar radiation; for those confined indoors a reference nutrient intake (RNI) of 10 micrograms (400 units) [as colecalciferol or ergocalciferol] daily was set. This RNI of 10 micrograms daily was also considered to be applicable to all persons aged 65 years or more and to pregnant and lactating women. RNIs were set for children up to the age of 3 years; dietary intake was considered unnecessary for older children. Mention was made that in order to achieve the above reference nutrient intakes, supplementation of the diet may actually be required and supplementation was also recommended for Asian [i.e. from the Indian subcontinent] women and children in the UK (see also Pregnancy and the Neonate, p. 2116.3). In the USA,[2] adequate intakes for vitamin D are: 5 micrograms (200 units) daily (as colecalciferol) for all persons from birth through to age 50 years, including pregnant or lactating women; 10 micrograms daily for adults aged 51 to 70 years; and 15 micrograms daily for those aged greater than 70 years. The tolerable upper intake level is 50 micrograms (2000 units) daily. The 2005 Dietary Guidelines for Americans (published jointly by the US Department of Health and Human Services, and the US Department of Agriculture) recommend that high-risk groups including the elderly, those with dark skin, and those exposed to insufficient UV radiation, consume daily intakes of 25 micrograms (1000 units) daily.[3] The definition of vitamin D deficiency and vitamin D insufficiency remains controversial in terms of serum vitamin D concentrations.[4,5] Because vitamin D insufficiency is considered to be common in northern latitudes,[5] and deficiency is increasing worldwide,[4] higher intakes than those mentioned above have been recommended. Some have called for the establishment of an estimated average requirement (EAR) in North America,[4] and estimate a recommended dietary allowance (RDA) of greater than 12.5 micrograms (500 units). Others[5] suggest that the adequate intake be increased to at least 20 to 25 micrograms (800 to 1000 units) daily. A risk assessment analysis concluded that the tolerable upper intake level of vitamin D could be increased to 250 micrograms (10 000 units) daily for the general healthy population.[6] There has been speculation that such supplementation might lead to broader benefits, on the grounds of suggested associations between lack of vitamin D and various cardiovascular, metabolic, and malignant diseases. Interestingly, a meta-analysis[7] of 18 randomised controlled studies in various conditions suggested a reduction in total mortality from any cause with vitamin D supplementation in doses of 7.5 to 50 micrograms (300 to 2000 units) daily. However, most of the studies included were in elderly patients at high risk of fractures, who often have low vitamin D levels.

The consensus of over 300 scientists from 23 countries at a vitamin D workshop was that governmental guidelines, in all countries, with respect to daily vitamin D requirements (to maintain bone health and health in general) were too low and did not reflect advances in vitamin D research over the preceding decade. Eating vitamin D-rich foods does not solve vitamin D deficiency for most adults; fortification of food should be significantly improved and implemented. Recommendations were made that blood concentrations of vitamin D should be at least 20 nanograms/mL, and that the tolerable upper intake level of 50 micrograms (2000 units) be re-evaluated in light of new data.[8]

For the view that colecalciferol is more potent than ergocalciferol, and should be the preferred form of vitamin D supplementation, see Administration, p. 2114.3.

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. 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)
3. US Department of Health and Human Services/US Department of Agriculture. Dietary Guidelines for Americans 2005. Available at: http://www.health.gov/DIETARYGUIDELINES/dga2005/document/pdf/DGA2005.pdf (accessed 10/09/07)
4. Whiting SJ, Calvo MS. Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement. *J Nutr* 2005; 135: 304–9.
5. Hanley DA, Davison KS. Vitamin D insufficiency in North America. *J Nutr* 2005; 135: 332–7.
6. Hathcock JN, *et al.* Risk assessment for vitamin D. *Am J Clin Nutr* 2007; 85: 6–18.
7. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; 167: 1730–7.
8. Norman AW, *et al.* 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol* 2007; 103: 204–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aderosol; Alpha D3; Dexiven; Findeclin Combi; Lotravel; Oravil; Ostelin; Raquiferol D3; Raquiferol; Raquitriol; Sterogyl; Trevix; Vita D; Zemplar; *Austral.*: Calcijex; Citrihexal†; Kosteo; Ostelin; OsteVit-D; Rocaltrol; Sical; Sitriol†; Zemplar; *Austria*: AT 10†; Bocatriol†; Bondiol; Calcijex; Etalpha; Laevovit D_3†; Oleovit D_3; Rocaltrol; Vi-De_3; Zemplar; *Belg.*: 1-Alpha; D-Cure; Dedrogyl; Rocaltrol; Silkis†; *Braz.*: Addera D3; Calcijex; Depura; Innosfen; Maxxi D3; Repocal D; Rocaltrol; Sigmacalcidol; Sigmatriol; Silkis†; Zemplar; *Canad.*: Calciferol; Calcijex; Citracal + D; D-Gel; D-Tabs; D-Vi-Sol; Drisdol†; Erdol; Euro D; One-Alpha; Osto-D2; Riva D†; Rocaltrol; Silkis; Zemplar†; *Chile*: Acuode; Etalpha; Fosamax Plus; Rocaltrol; Silkis†; Zemplar; *China*: Alfacan (法能); Alpha-D_3 (阿法迪三); Ao Si Hui (奥司惠); Bon-One (朗格旺); Calcijex (派纯); De Kai (得凯); Decostriol; Etalpha (依安凡); Faneng (法能)†; Gai Nuo Zhen (盖诺真); Gai San Chun (盖三淳); Hicalol (海卡洛); Liqing (立庆); Lonpryl (龙百利); Rocaltrol (罗盖全); Shuang Ye Hong (霜叶红); Silkis (秀可丝); Yan Di Nuo (延迪诺); Yingkangli (英康利); *Cz.*: Alpha D3; Calciferol; Calcijex†; Infadin†; OsteoD; Rocaltrol; Silkis; Tachystin†; Vigantol; Zemplar; *Denm.*: Detremin; Etalpha; Kalciferol†; One-Alpha; Zemplar; *Fin.*: Deetipat†; Detremin; Devitol; Divisun; Dygratyl; Etalpha; Jekovit; Silkis; Zemplar; *Fr.*: Adrigyl; Dedrogyl; Rocaltrol; Silkis; Sterogyl; Un-Alfa; Uvedose; Uvesterol D; Zymad; *Ger.*: AT 10; Bondiol; D_3 Vicotrat; Decostriol; Dedrei; Dedrogyl; Dekristol; Doss; EinsAlpha; Ospur D_3†; Osteotriol; Rocaltrol; Silkis; Tachystin†; Vigantol; Vigantoletten; Zemplar; *Gr.*: A-Calcid; A-Ostin-D3; Abbocalcijex; Alcidolin; Alestopor; Alfacalcil; Alfadel; Alpha D3; Alpha-Due†; Alpha-Plus; Alphabikal; Alphacal; Alphasidol; Alphazol; Antebe; Axelanol; Baludol; Biovit; Calcidrops; Calcitroject; *Calcodol-D3*; Calfadol; *Calinol*; Caltrioject; D-Triol; Decalcit; Dedrogyl†; Didrogyl; Dygratyl; Emarfen; Helposteol; Iasvest; Lifercal; Losefan; Mega-Alpha; One-Alpha; Ossidrol; Ostelin; Osteovile; Ostitriol; Otari; Silkis; Sterogyl; V-D-Bone; Vitocalcit; Votrace; Zemplar; *Hong Kong*: Alpha D3; Bocatriol†; Bon-One; Calcijex; Decostriol; One-Alpha; Rocaltrol; Silkis; Zemplar; *Hung.*: Alpha D3; Calcijex; Osteo D†; Rocaltrol; Silkis†; Tachystin†; Vigantol; Zemplar; *India*: Alfa Caps; Alfabol; Alfacal; Alfacip; Alfarich; Alfaset; Alpha D3†; Alphadol; Arachitol; Architol; Aristrol; Bio-D3; Calci-Best; Calcibest; Calcikind; Calcirol; Calcit SG; Caldikind; Calfa-D; Calosto; Caltrol; CCM; Celol; Cinvit-D; Devita; Dewin; Duracal; Fovit-D3; GR-Alfa; Kalzin; Minroset; One-Alpha; Ostriol; Rolsical; *Indon.*: Bon-One; Calcijex†; Calcit; Ecatrol; Kolkatriol; One-Alpha; Oscal; Osteofem; Ostovell; Ostriol; Rocaltrol; *Irl.*: AT 10; One-Alpha; Rocaltrol; Silkis; Zemplar; *Israel*: Alpha D3; Calcijex†; One-Alpha; Tevalfa; Zemplar; *Ital.*: Alpha D3; Atiten; Calcijex; Dediol; Deril; Dibase; Didrogyl; Difix; Diseon; Diserinal; Geniad; Ostelin; Ostidil-D3; Rocaltrol; Sefal; Silkis; Tridelta; Trikal†; Zemplar; *Jpn*: Alfarol; Hornel; Onealfa; Oxarol; Rocaltrol; *Malaysia*: Alpha D3; Bon-One; Bonky; Calcijex; Fairy ADE; One-Alpha; Osteocap; Rocaltrol; Roical; Zemplar; *Mex.*: Albrinol; Alfad; Altrical†; Altrol; Calciofem; Felipgel-P; Geldex; Lemyriol†; Nafartol; Rocaltrol†; Silkis; Tirocal; Triolan†; Valmetrol-3; Zemplar; Zygium†; *Neth.*: Calcijex†; Devaron; Dihydral; Etalpha; Rocaltrol; Silkis; Zemplar; *Norw.*: AFI-D_3; Detremin; Divisun; Etalpha; Rocaltrol; Silkis; Zemplar; *NZ*: CalD; One-Alpha; Rocaltrol; *Philipp.*: Alpha D3; Bon-One†; One-Alpha; Osteomeg†; Rocaltrol; Silkis; *Pol.*: Alfadiol; Calcijex†; Devikap; Devisol; Juvit D_3; One-Alpha; Rocaltrol†; Silkis†; Vigantol; Vigantoletten; Zemplar; *Port.*: Calcijex; Dedrogyl; Etalpha; Rocaltrol; Silkis; Vigantol; Zemplar; *Rus.*: Alpha D3 (Альфа Д3-тев); Aquadetrim (Аквадетрим); AT 10 (А Т 10); Etalpha (Этальфа); One-Alfa (Ван-Альфа); Osteotriol (Остеотрион); Oxidevit (Оксидевит); Rocaltrol (Рокальтрол); Tachystin (Тахистин)†; Vigantol (Вигантол); Zemplar (Земплар); *S.Afr.*: AT 10†; One-Alpha; Rocaltrol; *Singapore*: Alpha D3; Bon-One; Calcijex; One-Alpha†; Osteomed; Rasputin; Rocaltrol; Roical; Silkis; Zemplar; *Spain*: Calcijex†; Etalpha; Hidroferol; Rocaltrol; Silkis; Zemplar; *Swed.*: Detremin; Dygratyl; Etalpha; Rocaltrol; Zemplar; *Switz.*: AT 10†; Natecal D; Renatriol; Rocaltrol; Silkis; Vi-De_3; Zemplar; *Thai.*: Alpha D3; Alphadol†; Bon-One; Cacare; Calciferol; Calcit; Decostriol; Medi-Alpha; Meditrol; One-Alpha; Osteo D; Rocaltrol; *Turk.*: Alpha D3; Calcijex; Decostriol; Devit-3; Monovit D3; One-Alpha; Osivit-D3; Osteo-D; Rocaltrol; Vi-D3; Zemplar; *UAE*: Calciphar; *UK*: AT 10; Calcijex†; Desunin; Fultium-D_3; One-Alpha; Rocaltrol; Silkis; Vita-D3; Zemplar; *Ukr.*: Alpha D3 (Альфа Д3); Aquadetrim (Аквадетрим); *USA*:. Advanced D; Baby Drops; Calciferol; Calcijex; Calderol; D 400; D-Vita; D1000; D3-50; D_3 Dots; Ddrops; Decara; Delta-D; DHT; Drisdol; Enfamil D-Vi-Sol; Hectorol; High Potency D; Maximum D3; Replesta; Rocaltrol; Thera-D; Ultra Strength D; Vectical; Zemplar; *Venez.*: Alpha D3; Rocaltrol; Silkis; Zemplar.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Calcitriol Capsules; Calcium and Colecalciferol Tablets; Calcium and Ergocalciferol Tablets; Chewable Calcium and Colecalciferol Tablets; Chewable Calcium and Ergocalciferol Tablets; Colecalciferol Injection; Colecalciferol Tablets; Ergocalciferol Injection; Ergocalciferol Tablets; Paediatric Vitamins A, C and D Oral Drops;

BPC 1973: Calcium with Vitamin D Tablets; Vitamins A and D Capsules;

USP 36: Calcifediol Capsules; Calcitriol Injection; Calcium and Vitamin D with Minerals Tablets; Calcium with Vitamin D Tablets; Cholecalciferol Capsules; Dihydrotachysterol Capsules; Dihydrotachysterol Oral Solution; Dihydrotachysterol Tablets; Ergocalciferol Capsules; Ergocalciferol Oral Solution; Ergocalciferol Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; 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 Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins

with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Oleovitamin A and D Capsules; Oleovitamin A and D; Paricalcitol Injection.

Vitamin E Substances

Vitamina E. Витамины. Группы Е.
ATC — A11HA03.
ATC Vet — QA11HA03.

NOTE. The food additive number E306 is used for tocopherols.

Vitamin E is a generic term applied to a large number of natural or synthetic compounds. The most important substances are the **tocopherols** of which **alpha tocopherols** are the most active and widely distributed in nature; other naturally occurring tocopherols include beta, gamma, and delta tocopherols, but these are not used in therapeutics. The other group of compounds with vitamin E activity are the tocotrienols.

Alpha tocopherols occur naturally in the *d* optical isomer form, which is more active than the synthetic racemic *dl* form; for further details concerning the comparative activities of the different forms and isomers of vitamin E compounds, see under Units, below.

d-Alpha Tocopherol

d-Alfa Tokoferol; *RRR*-alpha-Tocophérol; *RRR*-alpha-Tocopherolum; *d*-Альфа-токоферол; Natural Alpha Tocopherol; Natural α-Tocopherol; D-α-Tocoferol; *d*-α-Tocopherol; *RRR*-α-Tocopherol; *RRR*-α-Tocopherolum; *RRR*-α-Tokoferol; *RRR*-α-Tokoferoli; *RRR*-α-Tokoferolis.
(+)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol.
$C_{29}H_{50}O_2$=430.7
CAS — 59-02-9.
UNII — N9PR3490H9.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows it under the title Vitamin E.

Ph. Eur. 8: (*RRR*-α-Tocopherol; *RRR*-Alpha-Tocopherol BP 2014). A clear, colourless, or yellowish-brown viscous oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in fatty oils. Store under an inert gas in airtight containers. Protect from light.

USP 36: (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is unstable to air and light, particularly in alkaline media. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store under an inert gas in airtight containers. Protect from light.

dl-Alpha Tocopherol

Synthetic α-Tocopherol; all-*rac*-α-Tocopherol; all-*rac*-α-Tokoferol; Alpha Tocopherol; *dl*-α-Tocopherol; dl-Альфа-токоферол; E307; int-*rac*-α-Tocopherolum; DL-α-Tocoferol; Synthetic Alpha Tocopherol; Tocoferolum Alfa; α-Tocopherol; α-Tocopherolum; α-Tokoferol; Tokoferol-alfa; tout-*rac*-α-Tocophérol; Visų racematų α-Tokoferolis; (±)-Alpha-Tocopherol.
(±)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol.
$C_{29}H_{50}O_2$=430.7
CAS — 10191-41-0.
UNII — H4N855PNZ1 (alpha tocopherol); 7QWA1RIO01 (dl-alpha tocopherol).

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn. US* allows it under the title Vitamin E.

Ph. Eur. 8: (all-*rac*-α-Tocopherol; all-*rac*-Alpha Tocopherol BP 2014). A clear, colourless or yellowish-brown viscous oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in fatty oils. Store under an inert gas. Protect from light.

USP 36: (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is unstable to air and light, particularly in alkaline media. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store under an inert gas in airtight containers. Protect from light.

d-Alpha Tocoferil Acetate

(+)-Alpha-Tocopherol Acetate; (+)-Alpha-Tocopheryl Acetate; *d*-Alpha Tocopheryl Acetate; *RRR*-alpha-Tocophéryle, acétate de; *RRR*-alpha-Tocopherylis acetas; d-Альфа-токоферола Ацетат; D-α-Tocoferilo, acetato de; Tocoferoli Alfa *RRR* Acetas; *RRR*-α-Tocopheroli Acetas; *d*-α-Tocopheryl Acetate; *RRR*-α-Tocopheryl Acetate; *RRR*-α-Tocopherylis Acetas; *RRR*-α-Tokoferilio acetatas; *RRR*-α-Tokoferol-acetát; Tokoferol-acetát alfa *RRR*; Tokoferol-alfa-*RRR*-acetát; *RRR*-α-Tokoferylacetat; *RRR*-α-Tokoferylu octan; *RRR*-α-Tokoferyylisetaatti.
(+)-α-Tocopherol acetate.
$C_{31}H_{52}O_3$=472.8
CAS — 58-95-7.
UNII — A7E6112E4N.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows it under the title Vitamin E.

Ph. Eur. 8: (*RRR*-α-Tocopheryl Acetate; *RRR*-Alpha-Tocopheryl Acetate BP 2014). A clear, colourless or slightly greenish-yellow, viscous oily liquid. Practically insoluble in water; soluble in alcohol; freely soluble in dehydrated alcohol, in acetone, and in fatty oils. Protect from light.

USP 36: (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It may solidify in the cold. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store in airtight containers. Protect from light.

dl-Alpha Tocoferil Acetate

tout-*rac*-α-Tocophéryle, acétate de; Acetato de *dl*-alfa-tocoferilo; all-*rac*-α-Tocopheryl Acetate; all-*rac*-α-Tokoferylu octan; Alpha Tocopheryl Acetate; *dl*-Alfa Tokoferil Asetat; *dl*-Alpha Tocopheryl Acetate; *dl*-α-Tocopheryl Acetate; dl-Альфа-токоферола Ацетат; int-*rac*-α-Tocopherylis acetas; DL-α-Tocoferilo, acetato de; Tocoferoli Alfa Acetas; α-Tocopherol Acetate; α-Tocopheroli Acetas; Tokoferol alfa-acetát; Tokoferolu octan; Visų racematų α-Tokoferilio acetatas; (±)-Alpha-Tocopherol acetate.
(±)-α-Tocopherol acetate.
$C_{31}H_{52}O_3$=472.8
CAS — 7695-91-2; 52225-20-4.
UNII — 9EBX80D2L0 (alpha tocoferil acetate); WR1WPI7EW8 (dl-alpha tocoferil acetate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn. US* allows it under the title Vitamin E.

Eur. also has a monograph for the concentrated powdered form.

Ph. Eur. 8: (all-*rac*-α-Tocopheryl Acetate; all-*rac*-Alpha Tocopheryl Acetate BP 2014). A clear, colourless or slightly greenish-yellow, viscous, oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, and in fatty oils. Protect from light.

Ph. Eur. 8: (α-Tocopheryl Acetate Concentrate (Powder Form); α-Tocopherylis Acetatis Pulvis; Alpha Tocopheryl Acetate Concentrate (Powder Form) BP 2014). It is prepared either by finely dispersing *dl*-alpha tocoferil acetate in a suitable carrier (e.g. gelatin, acacia, carbohydrates, lactoproteins, or a mixture of these) or by adsorbing *dl*-alpha tocoferil acetate on to silicic acid. The concentrate contains not less than 25% of *dl*-alpha tocoferil acetate. Almost white, yellowish, or light-brown small particles. Depending on the formulation, the powder may be practically insoluble in water or may swell or form a dispersion. Store in well-filled airtight containers. Protect from light.

USP 36: (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store in airtight containers. Protect from light.

d-Alpha Tocoferil Acid Succinate

d-Alpha-Tocopherol acid succinate; *d*-Alpha Tocopheryl Acid Succinate; *RRR*-alpha-Tocophéryle, hydrogénosuccinate de; *RRR*-alpha-Tocopherylis hydrogenosuccinas; d-Альфа Токоферола Сукцинат; D-α-Tocoferilo, succinato ácido; Succinato ácido de *d*-alfa-tocoferilo; Tocoferoli Alfa *RRR* Hydrogenosuccinas; *RRR*-α-Tocopheroli Hydrogenosuccinas; *d*-α-Tocopheryl Acid Succinate; *RRR*-α-Tocopheryl Hydrogen Succinate; *RRR*-α-Tocopherylis Hydrogenosuccinas; *RRR*-α-Tokoferilio-vandenilio sukcinatas; Tokoferol-alfa-*RRR*-hydrogen-sukcinát; *RRR*-α-Tokoferol-hidrogén-szukcinát; *RRR*-α-Tokoferylvätesuccinat; *RRR*-α-Tokoferyylivetysuksinaatti.
(+)-α-Tocopherol hydrogen succinate.
$C_{33}H_{54}O_5$=530.8
CAS — 4345-03-3.
UNII — LU4B53JYVE.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows it under the title Vitamin E.

US also includes Vitamin E Polyethylene Glycol Succinate, a mixture formed by the esterification of *d*-alpha tocoferil acid succinate with a macrogol.

Ph. Eur. 8: (*RRR*-α-Tocopheryl Hydrogen Succinate; *RRR*-Alpha Tocopheryl Hydrogen Succinate BP 2014). A white or almost white crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol and in acetone; very soluble in dichloromethane. Protect from light.

USP 36: (Vitamin E). A white, practically odourless, powder. M.p. about 75 degrees; it is unstable when held molten. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol, in acetone, in ether, and in vegetable oils; very soluble in chloroform; slightly soluble in alkaline solution. Store in airtight containers. Protect from light.

dl-Alpha Tocoferil Acid Succinate

Alpha Tocopheryl Hydrogen Succinate; DL-alpha-Tocophéryle, hydrogénosuccinate de; DL-alpha-Tocopherylis hydrogenosuccinas; *dl*-Alpha Tocopheryl Acid Succinate; *dl*-α-Tocopheryl Acid Succinate; dl-Альфа Токоферола Сукцинат; DL-α-Tocoferilo, succinato ácido; Succinato ácido de *dl*-alfa-tocoferilo; Tocoferoli Alfa Hydrogenosuccinas; DL-α-Tocopheroli Hydrogenosuccinas; DL-α-Tocopheryl Hydrogen Succinate; DL-α-tocopherylis Hydrogenosuccinas; DL-α-Tokoferilio-vandenilio sukcinatas; Tokoferol-alfa hydrogen sukcinát; DL-α-tokoferol-hidrogén-szukcinát; DL-α-Tokoferylvätesuccinat; DL-α-Tokoferyylivetysuksinaatti.
(±)-α-Tocopherol hydrogen succinate.
$C_{33}H_{54}O_5$=530.8
CAS — 17407-37-3.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows it under the title Vitamin E.

Ph. Eur. 8: (DL-α-Tocopheryl Hydrogen Succinate; Alpha Tocopheryl Hydrogen Succinate BP 2014). A white or almost white, crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol and in acetone; very soluble in dichloromethane. Protect from light.

USP 36: (Vitamin E). A white, practically odourless, powder. M.p. about 70 degrees; it is unstable when held molten. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol, in acetone, in ether, and in vegetable oils; very soluble in chloroform; slightly soluble in alkaline solution. Store in airtight containers. Protect from light.

Units

Though the potency of preparations of vitamin E is still sometimes expressed in units, the International Standard for vitamin E was discontinued in 1956. The International Unit was the activity contained in 1 mg of a standard preparation of *dl*-alpha-tocoferil acetate. Past editions of the USP have stated that in expressing vitamin E activity of tocopherol products, the following equivalents of 1 mg were to be used:

- *d*-alpha tocopherol, 1.49 units
- *dl*-alpha tocopherol, 1.1 units
- *d*-alpha tocoferil acetate, 1.36 units
- *dl*-alpha tocoferil acetate, 1 unit
- *d*-alpha tocoferil acid succinate, 1.21 units
- *dl*-alpha tocoferil acid succinate, 0.89 unit.

For dietary purposes, vitamin-E activity may now be expressed in terms of alpha tocopherol equivalents (α-TEs). One α-TE is the activity contained in:

- 1 mg of *d*-alpha tocopherol (natural alpha tocopherol; *RRR*-α-tocopherol)
- 1.4 mg *dl*-alpha tocopherol
- 1.1 mg *d*-alpha tocoferil acetate
- 1.5 mg *dl*-alpha tocoferil acetate
- 1.2 mg *d*-alpha tocoferil acid succinate
- 1.7 mg *dl*-alpha tocoferil acid succinate.

Uses and Administration

Vitamin E, a fat-soluble vitamin, prevents the oxidation of polyunsaturated fatty acids. It reacts with free radicals, which are the cause of oxidative damage to cell membranes, without the formation of another free radical in the process.

Vitamin E deficiency is rare but develops when the dietary intake is inadequate. In cystic fibrosis or cholestasis, malabsorption of fat may lead to a vitamin E deficiency; deficiency may also occur in abetalipoproteinaemia where there are abnormalities of lipid transport and malabsorption. In previously healthy adults malabsorption and low intake of vitamin E must continue for several years before signs of deficiency appear. The major signs of vitamin E deficiency are the development of myopathic and neurological disorders.

Vitamin E is used in the treatment and prevention of vitamin E deficiency. It is usually given orally, generally the preferred route, but has also been given by intramuscular or

intravenous routes. It may be given as *d*- or *dl*-alpha tocopherol or as the respective acetates or acid succinates.

Recommended doses vary, in part because of differences in the activity of different preparations; however, a daily dose of several times the recommended dietary allowance (RDA), or around 40 to 50 mg of *d*-alpha tocopherol, has been suggested for deficiency syndromes; somewhat higher daily doses have been given in cystic fibrosis (100 to 200 mg of *dl*-alpha tocoferil acetate, or about 67 to 135 mg of *d*-alpha tocopherol) and much higher daily doses in abetalipoproteinaemia (50 to 100 mg/kg of *dl*-alpha tocoferil acetate, or about 33 to 67 mg/kg *d*-alpha tocopherol).

For doses used in children, see Administration in Children, below.

Vitamin E has also been tried in many other disorders, for which the evidence of value is generally lacking (see Prophylaxis of Ischaemic Heart Disease, p. 2047.1, and Prophylaxis of Malignant Neoplasms, p. 2047.3).

Other substances with vitamin-E activity that have been used include *dl*-alpha tocoferil palmitate and tocofersolan (tocophersolan), a water-soluble substance which is *d*-alpha tocoferil acid succinate combined with a macrogol. Wheatgerm oil (p. 2647.1) is also widely used as a source of vitamin E.

Vitamin E is often used as an antoxidant in pharmaceutical manufacturing.

General reviews.

1. Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. *J Physiol Biochem* 2001; 57: 43–56.
2. Dutta A, Dutta SK. Vitamin E and its role in the prevention of atherosclerosis and carcinogenesis: a review. *J Am Coll Nutr* 2003; 22: 258–68.
3. Sung L, *et al.* Vitamin E: the evidence for multiple roles in cancer. *Nutr Cancer* 2003; 46: 1–14.
4. Zingg J-M, Azzi A. Non-antioxidant activities of vitamin E. *Curr Med Chem* 2004; 11: 1113–33.
5. Schneider C. Chemistry and biology of vitamin E. *Mol Nutr Food Res* 2005; 49: 7–30.
6. Mustacich DJ, *et al.* Vitamin E. *Vitam Horm* 2007; 76: 1–21.
7. Sen CK, *et al.* Tocotrienols: the emerging face of natural vitamin E. *Vitam Horm* 2007; 76: 203–61.
8. Clarke MW, *et al.* Vitamin E in human health and disease. *Crit Rev Clin Lab Sci* 2008; 45: 417–50.
9. Dolan Y, *et al.* No evidence supports vitamin E indiscriminate supplementation. *Biofactors* 2009; 35: 469–73.
10. Galli F, Azzi A. Present trends in vitamin E research. *Biofactors* 2010; 36: 33–42.

Administration in children. Vitamin E supplements are given to children with deficiency, such as that arising from fat malabsorption in cystic fibrosis and cholestatic liver disease; deficiency may also occur in abetalipoproteinaemia where there are abnormalities of lipid transport and malabsorption. The *BNFC* suggests the following doses expressed as *dl*-alpha tocoferil acetate, according to age:

Vitamin E deficiency

orally

- neonate: 10 mg/kg daily
- 1 month to 18 years: 2 to 10 mg/kg daily; up to 20 mg/kg has been used

Malabsorption in cystic fibrosis

orally

- 1 month to 1 year: 50 mg daily adjusted as necessary
- 1 to 12 years: 100 mg daily adjusted as necessary
- 12 to 18 years: as for adults, see Uses and Administration, p. 2119.3.

Cholestasis and severe liver disease

orally

- neonate: 10 mg/kg daily
- 1 month to 12 years: initially 100 mg daily, adjusted according to response; up to 200 mg/kg daily may be required
- 12 to 18 years: initially 200 mg daily, adjusted according to response; up to 200 mg/kg daily may be required

intramuscularly

- neonate: 10 mg/kg once monthly
- 1 month to 18 years: 10 mg/kg (maximum 100 mg) once monthly

For abetalipoproteinaemia in children, the recommended adult dose of 50 to 100 mg/kg *dl*-alpha tocoferil acetate daily is also used, although the higher dose of 100 mg/kg daily is suggested for neonates.

Vitamin E has also been tried in other perinatal disorders (below) such as intraventricular haemorrhage and retinopathy of prematurity (below).

Age-related macular degeneration. Dietary supplementation with antoxidants including vitamin E has been promoted for age-related macular degeneration. For further details, see under Betacarotene, p. 2051.2.

Chemotherapy-induced toxicity. A small pilot study[1] found that oral vitamin E 600 mg daily given during chemotherapy and for 3 months afterwards reduced chemotherapy-induced neuropathy in patients given regimens based on platinum (carboplatin or cisplatin), or paclitaxel, or both. (See also Effects on the Nervous System, under Cisplatin, p. 767.3.) The authors considered that similarities exist between neuropathy induced by cisplatin (and possibly paclitaxel) and that seen in vitamin E deficiency states, (see below). Oral vitamin E 300 mg daily alleviated palmar-plantar erythrodysesthesia in 5 patients given capecitabine and docetaxel.[2] In 4 of these patients, chemotherapy was continued without interruption or dose reduction. Improvement was generally noticed after 7 to 10 days of treatment.

1. Argyriou AA, *et al.* Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. *Neurology* 2005; 64: 26–31.
2. Kara IO, *et al.* Palmar-plantar erythrodysesthesia due to docetaxel-capecitabine therapy is treated with vitamin E without dose reduction. *Breast* 2006; 15: 414–24.

Deficiency states. Vitamin E deficiency may cause neurological damage characterised by sensory loss, ataxia and retinitis pigmentosa. In 2 patients with common variable immunodeficiency and an associated enteropathy, vitamin E deficiency developed. Treatment with intramuscular or oral vitamin E led to objective neurological improvement.[1]

1. Aslam A, *et al.* Vitamin E deficiency induced neurological disease in common variable immunodeficiency: two cases and a review of the literature of vitamin E deficiency. *Clin Immunol* 2004; 112: 24–9.

Dementia. A hypothesis that free radicals may trigger and maintain mechanisms responsible for neurodegeneration in Alzheimer's disease (p. 388.1) has prompted the investigation of antoxidant therapies.[1] Preliminary studies[1,2] have suggested that alpha tocopherol might possibly slow progression. A prospective cohort study found that self-administration of combined vitamin C and vitamin E was associated with a lower risk of vascular dementia in elderly men,[3] although no significant protective effect was seen against Alzheimer's disease. However, other studies have suggested that high intake of vitamins C and E, whether from diet[4] or supplements,[5] may reduce the risk of Alzheimer's disease. Yet another study suggested that dietary vitamin E, but not vitamin C, intake reduced the risk of Alzheimer's disease;[6] a population-based study found vitamin E intake from food and supplements to be associated with reduced cognitive decline.[7] US guidelines suggested[8] that oral vitamin E 1000 units twice daily be considered in patients with Alzheimer's disease in an attempt to slow progression of the disease. However, a large randomised study in patients with amnestic mild cognitive impairment found that vitamin E 2000 units daily provided no benefit over placebo in terms of probability of progression to Alzheimer's disease.[9] A meta-analysis[10] which included this study also found no evidence of efficacy, and suggested that vitamin E should not be recommended for treatment or prevention of cognitive impairment. Reviewers[11,12] have also recommended against the use of vitamin E for Alzheimer's disease.

1. Berman K, Brodaty H. Tocopherol (vitamin E) in Alzheimer's disease and other neurodegenerative disorders. *CNS Drugs* 2004; 18: 807–25.
2. Sano M, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997; 336: 1216–22.
3. Masaki KH, *et al.* Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology* 2000; 54: 1265–72.
4. Engelhart MJ, *et al.* Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA* 2002; 287: 3223–9.
5. Zandi PP, *et al.* Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County study. *Arch Neurol* 2004; 61: 82–8.
6. Morris MC, *et al.* Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA* 2002; 287: 3230–7.
7. Morris MC, *et al.* Vitamin E and cognitive decline in older persons. *Arch Neurol* 2002; 59: 1125–32.
8. Doody RS, *et al.* Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; 56: 1154–66. Also available at: http://www.neurology.org/cgi/reprint/56/9/1154.pdf (accessed 09/01/06)
9. Petersen RC, *et al.* Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; 352: 2379–88.
10. Isaac MGEKN, *et al.* Vitamin E for Alzheimer's disease and mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 30/01/09).
11. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Ann Pharmacother* 2005; 39: 2065–72.
12. Boothby LA, Doering PL. Vitamin C and vitamin E for Alzheimer's disease. *Ann Pharmacother* 2005; 39: 2073–80.

Ischaemic heart disease. For a discussion of studies involving vitamin E in the prophylaxis of ischaemic heart disease, see p. 2047.1.

Malignant neoplasms. For a discussion of studies involving vitamin E in the prophylaxis of malignant neoplasms, see p. 2047.3.

Motor neurone disease. A prospective analysis found that regular use of vitamin E supplements was associated with a decreased risk of amyotrophic lateral sclerosis.[1] However, further studies were considered necessary and significant evidence to support the benefit of antoxidants in motor neurone disease (p. 2605.2) is lacking.[2]

1. Ascherio A, *et al.* Vitamin E intake and risk of amyotrophic lateral sclerosis. *Ann Neurol* 2005; 57: 104–10.
2. Orrell RW, *et al.* Antioxidant treatment for amyotrophic lateral sclerosis/motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 20/06/08).

Muscle spasm. Vitamin E is one of several drugs that have been tried in the management of nocturnal cramps (p. 2014.1) but there is little convincing evidence to support its use.[1,2] It has, however, been found to have similar efficacy to quinine for haemodialysis-induced cramp (p. 1779.3).[3] A small study found the combination of vitamins E and C to be more effective than either vitamin alone for reducing haemodialysis-induced cramps; prolonged use was not evaluated.[4]

1. Connolly PS, *et al.* Treatment of nocturnal leg cramps: a crossover trial of quinine vs vitamin E. *Arch Intern Med* 1992; 152: 1877–80.
2. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; 59: 43234–52.
3. Roca AO, *et al.* Dialysis leg cramps: efficacy of quinine versus vitamin E. *ASAIO J* 1992; 38: M681–M685.
4. Khajehdehi P, *et al.* A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. *Nephrol Dial Transplant* 2001; 16: 1448–51.

Muscular dystrophies. Vitamin E substances have been used in some countries in the management of muscular dystrophies, but controlled studies[1] have failed to find any benefit.

1. Ørndahl G, *et al.* Functional deterioration and selenium-vitamin E treatment in myotonic dystrophy: a placebo-controlled study. *J Intern Med* 1994; 235: 205–10.

Parkinsonism. Vitamin E has been tried (as *dl*-alpha tocopherol) in an attempt to slow neurodegeneration in patients with Parkinson's disease (p. 889.1) but has proved ineffective.[1]

1. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; 328: 176–83.

Perinatal disorders. The primary biological action of vitamin E is known to be the protection of polyunsaturated fatty acids, and thus membranes, from oxidation. Two disorders that may particularly affect premature and very low birth-weight infants are *retinopathy of prematurity* (below) and *intraventricular haemorrhage* (p. 1128.3) and as both may have some association with the occurrence of excess oxygen or oxidant stress, there has been interest in the possibility that vitamin E might have a role in their prevention.

Pre-eclampsia. Although preliminary evidence has suggested[1] that women supplemented with vitamin E (with other supplements) may be at decreased risk of developing clinical pre-eclampsia (see Hypertension in Pregnancy, p. 1251.1), large studies[2,3] in women given combined vitamin C and vitamin E supplements failed to show any benefit.

1. Rumbold A, Crowther CA. Vitamin E supplementation in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 09/01/06).
2. Poston L, *et al.* Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 2006; 367: 1145–54.
3. Rumbold AR, *et al.* ACTS Study Group. Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med* 2006; 354: 1796–1806.

Respiratory-tract infections. A randomised study in elderly patients found that supplementation with vitamin E had no effect on the incidence of lower respiratory-tract infections in elderly nursing home residents, although there was some suggestion of benefit from supplementation on upper respiratory-tract infections, particularly the common cold.[1] In contrast, another study found that, among elderly non-institutionalised people with an acute respiratory-tract infection, vitamin E supplementation increased illness duration, number of symptoms, frequency of fever, and restricted activity.[2]

1. Meydani SN, *et al.* Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. *JAMA* 2004; 292: 828–36. Correction. *ibid.*: 1305.
2. Graat JM, *et al.* Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA* 2002; 288: 715–21.

Retinitis pigmentosa. Vitamin E has been tried in retinitis pigmentosa (p. 2101.1) with conflicting results.

Retinopathy of prematurity. Retinopathy of prematurity (retrolental fibroplasia) is a disease associated with immature vascularisation of the retina. Formation of retinal lesions may interfere with normal development, resulting in neovascularisation and fibrovascular proliferation. Some cases regress spontaneously but advanced cases can lead to tractional retinal detachment and loss of vision. The pathogenesis of retinopathy of prematurity is not clearly understood, but is likely to be multifactorial;[1,2] greater immaturity, lower birth-weight, and male gender are associated with more severe disease.[3]

After the acknowledgement of a link between retinopathy of prematurity and oxygen therapy, the use of oxygen was reduced and the incidence of this disorder declined. A subsequent rise in incidence probably reflected the increased survival rate of extremely premature infants due to improved neonatal care, and certainly, variations in incidence between countries, or indeed areas, may reflect varying levels of available postnatal care.[2] Despite extensive research (see p. 1801.3), a safe concentration of arterial oxygen has not been defined and antoxidants such as vitamin E have been used prophylactically for several decades. However, this use is controversial. Studies assessing the efficacy of vitamin E prophylaxis have not produced clear results.[4] Some considered that vitamin E prophylaxis had a beneficial effect and recommended[5] routine prophylaxis as soon as possible after birth for infants less than 1.5 kg. However, others feel that there are no data to support prophylaxis with vitamin E[4,6,7] and that antoxidants cannot be recommended for routine use.[1] The various studies have been re-evaluated by meta-analysis, the results of which suggest that vitamin E may reduce the incidence of stage 3+ retinopathy of prematurity,[8] a conclusion supported by a systematic review[9] which noted, however, that supplementation increased the risk of sepsis and could therefore not be recommended. The authors of the meta-analysis recommended that a well-controlled study should be conducted.[8] A systematic review of vitamin A supplementation in very low birth-weight infants concluded that vitamin A may reduce the incidence of retinopathy of prematurity, and that further investigation was warranted.[10]

Other agents tried for prophylaxis include penicillamine and antenatal dexamethasone, with some suggestion of benefit.[11,12] Reduction in ambient-light exposure did not alter the incidence of retinopathy of prematurity.[13,14] Inositol supplementation has also been tried, with conflicting results.[4]

Intravitreal injection of bevacizumab is under investigation for the management of severe retinopathy of prematurity.[15-17]

1. Holmström G. Retinopathy of prematurity. *BMJ* 1993; **307**: 694–5.
2. Wheatley CM, *et al.* Retinopathy of prematurity: recent advances in our understanding. *Arch Dis Child Fetal Neonatal Ed* 2002; **87**: F78–F82.
3. Darlow BA, *et al.* Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. *Pediatrics* 2005; **115**: 990–6.
4. Reynolds JD. The management of retinopathy of prematurity. *Paediatr Drugs* 2001; **3**: 263–72.
5. Johnson L, *et al.* Effect of sustained pharmacologic vitamin E levels on incidence and severity of retinopathy of prematurity: a controlled clinical trial. *J Pediatr* 1989; **114**: 827–38.
6. Law MR, *et al.* Is routine vitamin E administration justified in very low-birthweight infants? *Dev Med Child Neurol* 1990; **32**: 442–50.
7. Ehrenkranz RA. Vitamin E and retinopathy of prematurity: still controversial. *J Pediatr* 1989; **114**: 801–3.
8. Raju TNK, *et al.* Vitamin E prophylaxis to reduce retinopathy of prematurity: a reappraisal of published trials. *J Pediatr* 1997; **131**: 844–50.
9. Brion LP, *et al.* Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 20/06/08).
10. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 14/03/08).
11. Higgins RD, *et al.* Antenatal dexamethasone and decreased severity of retinopathy of prematurity. *Arch Ophthalmol* 1998; **116**: 601–5.
12. Phelps DL, *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 09/01/06).
13. Reynolds JD, *et al.* Lack of efficacy of light reduction in preventing retinopathy of prematurity. *N Engl J Med* 1998; **338**: 1572–6.
14. Phelps DL, Watts JL. Early light reduction for preventing retinopathy of prematurity in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).
15. Mintz-Hittner HA, Kuffel RR. Intravitreal injection of bevacizumab (Avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. *Retina* 2008; **28**: 831–8.
16. Kusaka S, *et al.* Efficacy of intravitreal injection of bevacizumab for severe retinopathy of prematurity: a pilot study. *Br J Ophthalmol* 2008; **92**: 1450–5.
17. Quiroz-Mercado H, *et al.* Antiangiogenic therapy with intravitreal bevacizumab for retinopathy of prematurity. *Retina* 2008; **28** (suppl): S19–S25. Correction. *ibid.* 2009; **29**: 127.

Tardive dyskinesia. Reviews[1,2] on the use of vitamin E in the management of antipsychotic-induced tardive dyskinesia (see under Extrapyramidal Disorders, p. 1049.3) concluded that evidence of benefit has generally come from small studies with methodological problems. One review[1] concluded that whereas vitamin E may protect against deterioration of tardive dyskinesia there was no evidence that it produced symptomatic improvement. It was suggested[2] that vitamin E therapy may be most beneficial in those patients with tardive dyskinesia of less than 5-years duration. Some recommend vitamin E as a treatment option in patients with newly diagnosed disease.[3] Further large-scale studies are required to establish its place in treatment.

1. McGrath J, Soares-Weiser K. Vitamin E for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 09/01/06).
2. Boomershine KR, *et al.* Vitamin E in the treatment of tardive dyskinesia. *Ann Pharmacother* 1999; **33**: 1195–1202.
3. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Ann Pharmacother* 2005; **39**: 2065–72.

Adverse Effects and Precautions

Vitamin E is usually well tolerated. Large doses may cause diarrhoea, abdominal pain, and other gastrointestinal disturbances, and have also been reported to cause blurred vision, dizziness, fatigue and weakness. Contact dermatitis has occurred after topical application.

Large doses of vitamin E have been reported to increase bleeding tendency in vitamin-K deficient patients such as those taking oral anticoagulants. However, it has also been suggested that it may increase the risk of thrombosis in some patients, such as those taking oestrogens. The clinical significance of these effects is not known.

A higher incidence of necrotising enterocolitis has been noted in premature infants weighing less than 1.5 kg treated with vitamin E.

Carcinogenicity. For mention of an *increased* incidence of second primary cancers and reduced cancer-free survival in patients with head and neck cancer receiving vitamin E (and betacarotene initially), see Prophylaxis of Malignant Neoplasms, p. 2047.3.

Effects on mortality. While some studies of antoxidants, including vitamin E, have suggested beneficial effects on the progression of cardiovascular disease and cancer, other studies (including large randomised studies such as the Women's Health Study[1]) have shown little or no effect.[2] Vitamin E may even cause an increased risk of heart failure, or incidence of some cancers (see Prophylaxis of Ischaemic Heart Disease, p. 2047.1, and Prophylaxis of Malignant Neoplasms, p. 2047.3). A meta-analysis[3] and a systematic review[4] of vitamin E supplementation found no benefit in terms of mortality. Another meta-analysis[5] found no effect for vitamin E supplementation on all-cause mortality overall. However, in dose-response analysis, high-dosage vitamin E (greater than 400 units daily) showed a significantly increased risk; there was some suggestion of a decreased risk with low doses (less than 400 units daily); all-cause mortality progressively increased for doses greater than 150 units daily. (Such an effect was not seen in the Women's Health Study, in which participants received 600 units on alternate days.) Some have commented[6] that the meta-analysis may not have isolated the effects of vitamin E, since in many of the trials studied, other nutritional supplements had been given, including betacarotene, itself possibly associated with an increased risk of death; however, the use of high-dose vitamin E was considered unjustified. A systematic review of antoxidant supplementation found that vitamin E, either singly or with other antoxidants, increased mortality.[7] A large cohort study in a population aged 65 years or older, after adjustment for age and sex, found that there was no association between vitamin E use and mortality. However, mortality was increased in vitamin E users who had a history of cardiovascular disease, or who were taking nitrates, warfarin, and diuretics. There was a consistent trend towards reduced mortality in vitamin E users without cardiovascular disease or taking these drugs. The authors concluded that vitamin E should be used with caution in those with cardiovascular disease, and that further investigation of the potential interaction between vitamin E and particular drugs was warranted.[8]

1. Lee I-M, *et al.* Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005; **294**: 56–65.
2. Brown BG, Crowley J. Is there any hope for vitamin E? *JAMA* 2005; **293**: 1387–90.
3. Vivekananthan DP, *et al.* Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003; **361**: 2017–23.
4. Shekelle PG, *et al.* Effect of supplemental vitamin E for the prevention and treatment of cardiovascular disease. *J Gen Intern Med* 2004; **19**: 380–9.
5. Miller ER, *et al.* Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; **142**: 37–46.
6. Greenberg ER. Vitamin E supplements: good in theory, but is the theory good? *Ann Intern Med* 2005; **142**: 75–6.
7. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).
8. Hayden KM, *et al.* Cache County Investigators. Risk of mortality with vitamin E supplements: the Cache County study. *Am J Med* 2007; **120**: 180–4.

Neonatal toxicity. For a review and discussion of liver and kidney toxicity in premature neonates associated with an intravenous preparation of vitamin E (E-Ferol) and attributed to the inclusion of polysorbates, see Effects in Infants, p. 2204.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vitamin E substances 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 07/10/11)

Interactions

Various drugs may interfere with the absorption of vitamin E including colestyramine, colestipol, and orlistat. High doses of vitamin E may increase the effects of oral anticoagulants.

Pharmacokinetics

Absorption of vitamin E from the gastrointestinal tract is dependent on the presence of bile and on normal pancreatic function. The amount of vitamin E absorbed varies widely between about 20% and 80% and appears to decrease as the dose is increased. It enters the blood via the chylomicrons in the lymph and is bound to beta lipoproteins. It is widely distributed to all tissues, and stored in adipose tissue. Some vitamin E is metabolised in the liver to glucuronides of tocopheronic acid and its γ-lactone. Some is excreted in the urine, but most of a dose is slowly excreted in the bile. Vitamin E appears in breast milk but is poorly transferred across the placenta.

Human Requirements

The daily requirement of vitamin E has not been clearly defined but is probably about 3 to 12 mg of *d*-alpha tocopherol or the equivalent of other vitamin E substances. Requirements increase with increased dietary amounts of polyunsaturated fatty acids. There appears to be no evidence that supplements are required in subjects on balanced diets.

Vitamin E is widely distributed in food. The richest sources are vegetable oils especially wheat-germ oil (p. 2647.1), sunflower oil, and cottonseed oil; cereals and nuts are also good sources. Significant losses of vitamin E from food may occur during cooking and storage.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI—see p. 2046.1) nor an estimated average requirement (EAR) has been set for vitamin E although daily intakes of 4 mg and 3 mg α-tocopherol equivalents (see under Units, p. 2119.3) were considered adequate for men and women, respectively.[1] The Expert Group on Vitamins and Minerals[2] have established a safe upper level (SUL) for vitamin E of 800 units or 540 mg of *d*-alpha tocopherol daily.

In the USA the recommended dietary allowance for adults is 15 mg daily of alpha tocopherol, and the tolerable upper intake level is 1 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. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 09/01/06)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids*. Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antioxidante Natural†; E-devit Protectora†; Ephynal; Etec; Evion; Tonovital E†; *Austral.*: Chew-E†; Dal-E†; Mega E; Micelle E†; Natural E†; Water Soluble E†; *Austria*: Avigilen; Etocovit; Evitol; Tocovenos†; *Belg.*: Ephynal†; Optovit E; *Braz.*: Bio E; E Plus†; E-Radicaps; E-Tabs; Emama; Ephynal; Fonto-Vit E†; Fort E; Teutovit-E; Vieta; Vita-E; Vitizin E; Zirvit E; *Canad.*: Aquasol E†; E-Prime†; Kyolic Formula 106†; Novo E†; *Chile*: Crevet-E; Egogyn; Etec; *China*: Su Le Kang (苏乐康); *Cz.*: Erevit; Vedrop; *Denm.*: E-Vitamin; Vedrop; *Fin.*: Bio-E-Vitamin; Equiday; Ido-E†; *Fr.*: Dermorelle; Toco; Tocolion; Tocopa; Vedrop; *Ger.*: Antioxidans E; Detulin†; Eusovit; Evion†; Flexal Vitamin E†; Malton E; Mowivit; Optovit; Sanavitan S†; Spondyvit†; Tocorell; Uno-Vit†; Vedrop; Vitazell E; *Gr.*: E-Vicotrat; Ephynal; Eviol; Evion; Evit; *Hong Kong*: Keri Vit E†; Myra 300-E†; Natopherol†; Super E†; Topher-E†; *India*: Bio-8888; Bio-E; Covita; E-Cap; Edge; EEE; Ensules; Ephynal; Etoplex; Evion; Evit; Evitam; Evitop; Glyvion; Monovit-EN; Novee; Ocuvit; *Indon.*: Bio-E; Dalfarol; Edoti; Erpha Vit E; Evion; Evipon; Lanturol; Natopherol; Natur-E; Naturol; Orginal E; Prima-E; Proxidan; Santa-E; Tocopherine†; Vinpo-E; Vitaferol; *Irl.*: Vedrop; *Israel*: Evitex; Evitol; *Ital.*: Armilla; Ephynal; Evasen Crema; Evion; Natovit; Rigentex; Sursum; Vedrop; *Jpn*: Juvela; *Malaysia*: Citrex Vitamin E; Enat; Fairy ADE; Natopherol; Toco-E; Vitamin E.F.C.; *Mex.*: E-Fertoc; Egrin†; EPH; Eugerminol; Ixopolet; Revitare E; Vit-E-

The symbol † denotes a preparation no longer actively marketed

Far; *Neth.*: Vedrop; *Norw.*: Bio-E; Ido-E†; Nycoplus E-vitamin; Vedrop; *NZ*: Micelle E†; *Philipp.*: Enat; Enervon-E; Evion; Integra-E; Lexivit-E; Myra; Zyme; *Pol.*: Dermovit E; Tokovit E; Vedrop; Vitole E†; *Port.*: Ve; Vedrop; *Rus.*: Evitol (Эвитол); *S. Afr.*: Ephynal†; Vitaforce E†; *Singapore*: Enat; Natopherol; Naturee; Rosken Skin Repair Vitamin E; *Spain*: Auxina E; Ephynal; Vedrop; *Swed.*: E-vidon†; E-vimin; Ido-E†; Vedrop; *Switz.*: ecobiosan†; Ephynal; Evit; Optovit†; *Thai.*: Bio-E; Blackmores Bio E; E-Drops; Nat E; Patar E-400; Tupper-E; *Turk.*: E-400; Eforol; Ephynal; Evicap; Evigen; Evon; Grandpherol; Natural E†; *UK*: Ephynal; Prairie Gold; Vedrop; Vita-E; *Ukr.*: Enat (Энат); *USA*: Aqua-E; Aquasol E; Aquavit-E; E-Gems; E-Oil; GRX Vitamin E; Natural E; Nutr-E-Sol; Promega; Vita-Plus E; Vitec; *Venez.*: Best; Egogyn; Epol; Missecap; Nat-E; Vit-E-Nat; Vit-E-Var; Vitae; Viteral.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. *Ger.*: Infi-Symphytum; NeyChon Nr 68; NeyDil Nr 66†; NeyGero Nr 64; NeyGeront Vitalkapsein A; NeyLing Nr 66.

Pharmacopoeial Preparations
BP 2014: Alpha Tocopheryl Succinate Tablets;
USNF 31: Tocopherols Excipient;
USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; 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 Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Vitamin E Capsules; Vitamin E Preparation.

Vitamin K Substances

Vitamina K; Витамины Группы К

The term vitamin K is used for a range of naphthoquinone compounds that includes: acetomenaphthone, menadiol, menadione, menatetrenone, and phytomenadione.

Acetomenaphthone *(BAN)*

Acetomenadione; Acetomenaftona; Acetomenaph.; Menadiol Diacetate; Vitamin K_4 Diacetate; Ацетоменафтон.
2-Methyl-1,4-naphthylene diacetate.
$C_{15}H_{14}O_4$=258.3
CAS — 573-20-6.
UNII — DWG8UZD9HT.

Pharmacopoeias. In *Chin.*

Menadiol Sodium Phosphate *(BANM)*

Menadiol fosfato sódico de; Menadiol Sodium Diphosphate; Menadiolum Solubile; Vitamin K_4 Sodium Phosphate.
2-Methylnaphthalene-1,4-diyl bis(disodium phosphate) hexahydrate.
$C_{11}H_8Na_4O_8P_2.6H_2O$=530.2
CAS — 481-85-6 (menadiol); 131-13-5 (anhydrous menadiol sodium phosphate); 6700-42-1 (menadiol sodium phosphate hexahydrate); 84-98-0 (menadiol diphosphate).
UNII — ZOVL75830W (menadiol sodium phosphate); GRL65FEU3T (menadiol diphosphate).

NOTE. Menadiol Potassium Sulfate (Potassium Menaphthosulfate) is *BAN* and Menadiol Sodium Sulfate is *rINN*.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Menadiol Sodium Phosphate). A white to pink, hygroscopic, crystalline powder with a characteristic odour. Very soluble in water; practically insoluble in alcohol.

USP 36: (Menadiol Sodium Diphosphate). A white to pink, hygroscopic, powder having a characteristic odour. Very soluble in water; insoluble in alcohol. Its solutions in water are neutral or slightly alkaline to litmus having a pH of about 8. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Menadione *(BAN)*

Menadion; Menadiona; Menadionas; Ménadione; Menadionum; Menadionum; Menaftona; Menaph.; Menaphthene; Menaphthone; Methylnaphthochinonum; Vitamin K_3; Vitamina K_3; Менадион.
2-Methyl-1,4-naphthoquinone.
$C_{11}H_8O_2$=172.2
CAS — 58-27-5.
ATC — B02BA02.
ATC Vet — QB02BA02.
UNII — 723X6CXY5.

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

Ph. Eur. 8: (Menadione). A pale yellow crystalline powder. It is unstable in light. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in toluene. Protect from light.

USP 36: (Menadione). A bright yellow, practically odourless, crystalline powder. It is affected by sunlight. Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 50 of vegetable oils, and 1 in 10 of benzene; sparingly soluble in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Handling. Menadione powder is irritating to the respiratory tract and to the skin. The alcoholic solution has vesicant properties.

Menadione Sodium Bisulfite *(BANM, rINN)*

Bisulfito sódico de menadiona; Kavitanum; Menadiol Sodyum Bisülfit; Menadiona, bisulfito sódico de; Ménadione, Bisulfite Sodique de; Menadione Sodium Bisulphite; Menadioni Natrii Bisulfis; Menadioninatriumbisulfitit; Menadionnatriumbisulfit; Menadionu wodorosiarczyn sodowy; Menaph. Sod. Bisulphite; Menaphthone Sodium Bisulphite; Methylnaphthochinonumnatrium Bisulfurosum; Vikasolum; Vitamin K_3 Sodium Bisulphite; Менадиона Натрия Бисульфит.
Sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxonaphthalene-2-sulphonate trihydrate.
$C_{11}H_8O_2NaHSO_3.3H_2O$=330.3
CAS — 130-37-0 (anhydrous menadione sodium bisulfite); 6147-37-1 (menadione sodium bisulfite trihydrate).
UNII — 6XF3C2HK77.

Pharmacopoeias. In *Chin.* and *Pol.*

Menatetrenone *(rINN)*

E-3100; Ea-0167; Menaquinone 4; Menaquinone K4; Menaquinone-4; Menatetren; Menatetrenona; Ménatétrénone; Menatetrenonum; MK-4; Vitamin $K_{2(20)}$; Vitamin MK 4; Менатетренон.
2-Methyl-3-(3,7,11,15-tetramethyl-2,6,10,14-hexadeca-tetraenyl)-1,4-naphthoquinone.
$C_{31}H_{40}O_2$=444.7
CAS — 863-61-6.
UNII — 27Y876D139.

Pharmacopoeias. In *Jpn.*

Phytomenadione *(BAN, rINN)*

Filoquinona; Fitomenadion; Fitomenadiona; Fitomenadionas; Fitonadiona; Fytomenadion; Fytomenadioni; Methylphytylnaphthochinonum; Phylloquinone; Phytomenad.; Phytomenadion; Phytoménadione; Phytomenadionum; Phytonadione; Vitamin K_1; Vitamina K_1; Фитоменадион.
2-Methyl-3-[3,7,11,15-tetramethylhexadec-2-enyl] naphthalene-1,4-dione.
$C_{31}H_{46}O_2$=450.7
CAS — 84-80-0.
ATC — B02BA01.
ATC Vet — QB02BA01.
UNII — A034SE7857.

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

Ph. Eur. 8: (Phytomenadione). A mixture of the *trans* (*E*) and *cis* (*Z*) isomers. It contains not less than 75% of *trans*-phytomenadione, and also allows not more than 4% of *trans*-epoxyphytomenadione.

A clear, intense yellow, viscous, oily liquid, which decomposes on exposure to actinic light. Practically insoluble in water; sparingly soluble in alcohol; miscible with fatty oils. Protect from light.

USP 36: (Phytonadione). A mixture of the *E* and *Z* isomers. It contains not more than 21% of the *Z* isomer. A clear, yellow to amber, very viscous, odourless or practically odourless, liquid. It is stable in air, but decomposes on exposure to sunlight. Insoluble in water; slightly soluble in alcohol; soluble in dehydrated alcohol, in chloroform, in ether, in vegetable oils, and in benzene. Store in airtight containers. Protect from light.

Stability. A polyoxyl castor oil formulation of phytomenadione was stable for at least 30 days at room temperature when repackaged in amber glass dropper bottles.[1] When refrigerated at 4 degrees to 8 degrees, it was stable in both plastic and amber glass bottles.

1. Wong VK, Ho PC. Stability of Konakion repacked in dropper bottles for oral administration. *Aust J Hosp Pharm* 1996; 26: 641–4.

Uses and Administration

Vitamin K is an essential cofactor in the hepatic synthesis of prothrombin (factor II) and other blood clotting factors (factors VII, IX, and X, and proteins C and S) and in the function of proteins such as osteocalcin important for bone development.

Vitamin K deficiency may develop in neonates (see Vitamin K Deficiency Bleeding, p. 2123.2), but is uncommon in adults, although it may occur in patients with malabsorption syndromes, obstructive jaundice or hepatic disease. Deficiency leads to the development of hypoprothrombinaemia, in which the clotting time of the blood is prolonged and spontaneous bleeding can occur. Coumarin anticoagulants interfere with vitamin K metabolism, and their effects can be antagonised by giving vitamin K.

Vitamin K compounds are used in the treatment and prevention of haemorrhage associated with vitamin K deficiency. The dose of vitamin K should be carefully controlled by prothrombin-time estimations.

Phytomenadione is a naturally occurring vitamin K substance. It is the only vitamin K compound used to reverse hypoprothrombinaemia and haemorrhage caused by anticoagulant therapy. It is not effective as a heparin antidote. For over-anticoagulation, the dose depends on the international normalised ratio (INR) and the degree of haemorrhage. Typical doses of phytomenadione are 0.5 to 10 mg by slow intravenous injection or up to 5 mg orally (see also Over-anticoagulation, p. 2123.1). Depending on the solubilising agents used, some formulations of phytomenadione are more suitable for intravenous use than others, and dosage details vary. Phytomenadione has also been used in hypoprothrombinaemia due to certain cephalosporins (see Cefamandole, Adverse Effects, p. 236.3).

For doses of vitamin K used in children, see Administration in Children, below.

Menadiol sodium phosphate is a water-soluble derivative of menadione, a synthetic lipid-soluble vitamin K analogue. It may be used for the prevention of vitamin K deficiency in patients with malabsorption syndromes in whom oral phytomenadione may be inefficiently absorbed. It is given in usual oral doses equivalent to 10 to 40 mg of menadiol phosphate daily.

Menadiol dibutyrate has also been used; *menatetrenone* is used in the management of osteoporosis. *Acetomenaphthone* has been used in preparations promoted for the relief of chilblains.

General reviews.
1. Shearer MJ. Vitamin K. *Lancet* 1995; 345: 229–34.
2. Vermeer C, Schurgers LJ. A comprehensive review of vitamin K and vitamin K antagonists. *Hematol Oncol Clin North Am* 2000; 14: 339–53.
3. Vermeer C, *et al.* Beyond deficiency: potential benefits of increased intakes of vitamin K for bone and vascular health. *Eur J Nutr* 2004; 43: 325–35.
4. Van Winckel M, *et al.* Vitamin K, an update for the paediatrician. *Eur J Pediatr* 2009; 168: 127–34.

Administration in children. Vitamin K deficiency can occur in children with fat malabsorption, particularly in those with cholestasis or severe liver disease. Neonates are relatively deficient in vitamin K and are at risk of bleeding if not supplemented, see Vitamin K Deficiency Bleeding p. 2123.2. Vitamin K is also used to reverse over-anticoagulation in children (see p. 2123.1).

Phytomenadione is the only vitamin K compound used to reverse hypoprothrombinaemia and haemorrhage caused by coumarin anticoagulants. For over-anticoagulation in children, specialist advice is recommended; the dose depends on the international normalised ratio (INR), the degree of haemorrhage, and whether continued anticoagulation is required. The *BNFC* suggests the following phytomenadione doses in children aged 1 month to 18 years:
- no significant bleeding or if continued anticoagulation required: intravenous injection of 15 to 30 micrograms/kg (maximum 1 mg) as a single dose, repeated as necessary
- significant bleeding or if continued anticoagulation no required: intravenous injection of 250 to 300 micrograms/kg (maximum 10 mg) as a single dose. UK licensed product information allows this dose to be repeated if response is inadequate after 2 to 6 hours

In less severe cases, an oral dose of phytomenadione 5 or 10 mg has been used in children.

The water-soluble derivative, menadiol sodium phosphate, is given as supplementation in vitamin K malabsorption. The *BNFC* suggests the following oral doses, expressed as menadiol phosphate, according to age:
- 1 to 12 years: 5 to 10 mg daily
- 12 to 18 years: 10 to 20 mg daily

In neonates with biliary atresia and liver disease oral phytomenadione 1 mg daily may be given.

For discussion of the use of vitamin K in the management of neonatal intraventricular haemorrhage, see p. 2123.1.

Action. References to the action of vitamin K and the role of vitamin K-dependent coagulation proteins and carboxyglutamate-containing proteins such as osteocalcin.

1. Friedman PA. Vitamin K-dependent proteins. *N Engl J Med* 1984; 310: 1458–60.
2. Rick ME. Protein C and protein S: vitamin K-dependent inhibitors of blood coagulation. *JAMA* 1990; 263: 701–3.
3. Nelsestuen GL, *et al.* Vitamin K-dependent proteins. *Vitam Horm* 2000; 58: 355–89.
4. Saxena SP, *et al.* Novel vitamin K-dependent pathways regulating cell survival. *Apoptosis* 2001; 6: 57–68.

Malignant neoplasms. In a small study in women with viral cirrhosis of the liver to establish the effects of vitamin K on bone loss, those given menatetrenone were found to have a lower incidence of hepatocellular carcinoma; larger controlled studies were advocated, with prevention of carcinoma by menatetrenone as a primary end-point.[1] Another study[2] reported reduced recurrence of hepatocellular carcinoma in patients given menatetrenone.

1. Habu D, *et al.* Role of vitamin K_2 in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. *JAMA* 2004; 292: 358–61.
2. Mizuta T, Ozaki I. Hepatocellular carcinoma and vitamin K. *Vitam Horm* 2008; 78: 435–42.

Neonatal intraventricular haemorrhage. Vitamin K crosses the placenta slowly and to a limited extent, but sufficiently to warrant studies to assess whether giving phytomenadione to the mother can reduce the incidence or severity of intraventricular haemorrhage (p. 1128.3) in the preterm neonate. Studies have shown conflicting results. A systematic review concluded that vitamin K given to the mother before birth did not significantly prevent periventricular haemorrhage, and could not be recommended for routine clinical use.[1]

1. Crowther CA, *et al.* Vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 27/05/10).

Osteoporosis. The effects of vitamin K on bone, and its role in osteoporosis (p. 1168.1) have been reviewed.[1-5] It is widely prescribed for the management of osteoporosis in Japan.[3] A reduced risk of vertebral[6] and nonvertebral[7] fracture has been reported from 2 studies in postmenopausal women given menatetrenone 45 mg daily by mouth. Vitamin K_2 (menaquinones such as menatetrenone) appears to have more marked effects on bone than vitamin K_1 (phytomenadione).[3] Oral phytomenadione 5 mg daily for 2 to 4 years did not protect against age-related decline in bone mineral density (BMD) in postmenopausal Canadian women with osteopenia, although some protection against fractures (as well as a reduction in the incidence of cancer) was reported.[8] A systematic review[9] to assess whether vitamin K supplementation can reduce bone loss and prevent fractures identified 13 studies with data on bone loss; 7 reported fracture data. Most studies were conducted in Japan among postmenopausal women. Vitamin K supplements increased BMD in all but 1 study. Meta-analyses of the 7 studies with fracture data showed a reduced fracture incidence with menatetrenone supplementation, especially at the hip. The authors advised caution in interpretation of the data, since the studies were not designed to show fracture effects, and quality of many of the trials was poor. In addition, dietary differences in Japan might confound findings. While patients at risk of fracture should be encouraged to consume a diet high in vitamin K, routine supplementation is not justified until these results can be confirmed in a large randomised study with fracture as a primary outcome.

1. Iwamoto J, *et al.* Effects of vitamin K2 on osteoporosis. *Curr Pharm Des* 2004; 10: 2557–76.
2. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *Am J Health-Syst Pharm* 2005; 62: 1574–81.
3. Plaza SM, Lamson DW. Vitamin K2 in bone metabolism and osteoporosis. *Altern Med Rev* 2005; 10: 24–35.
4. Bügel S. Vitamin K and bone health in adult humans. *Vitam Horm* 2008; 78: 393–416.
5. Shea MK, Booth SL. Update on the role of vitamin K in skeletal health. *Nutr Rev* 2008; 66: 549–57.
6. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. *Am J Med* 2004; 117: 549–55.
7. Sato Y, *et al.* Menatetrenone and vitamin D2 with calcium supplements prevent nonvertebral fracture in elderly women with Alzheimer's disease. *Bone* 2005; 36: 61–8.
8. Cheung AM, *et al.* Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. *PLoS Med* 2008; 5: e196. Available at: http://medicine.plosjournals.org/archive/1549-1676/5/10/pdf/10.1371_journal.pmed.0050196-L.pdf (accessed 13/03/09)
9. Cockayne S, *et al.* Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; 166: 1256–61.

Over-anticoagulation. Doses of vitamin K for over-anticoagulation with warfarin have traditionally been large, and this continues to be reflected in licensed product information for these products, where recommended oral or parenteral doses range from 2.5 to 25 mg initially, with a maximum dose of 40 to 50 mg. However, large doses of vitamin K may result in overcorrection, and increase the delay before resumed anticoagulant therapy becomes effective. In addition, the time to onset of action is a minimum of 1 to 2 hours, irrespective of dose. There is increasing evidence that lower doses of vitamin K are effective in over-anticoagulation,[1-3] and this is reflected in current guidelines (see Treatment of Adverse Effects of Warfarin, p. 1529.1). The use of vitamin K lowers the elevated INR faster than witholding warfarin alone. However, for patients on phenprocoumon, vitamin K had insufficient effect, and no benefit for those on acenocoumarol; stopping therapy is more effective.[3] The route by which vitamin K is given may also be significant. A meta-analysis[4] of studies of vitamin K for the treatment of over-anticoagulation found that oral or intravenous vitamin K therapy was more effective for warfarin than simply stopping the anticoagulant; however, subcutaneous therapy was not effective. A review[5] noted that over-anticoagulated patients present with a wide range of INR values, and may respond differently to fixed dosing regimens of vitamin K, leaving them outside their target INR 24 hours after treatment and at risk for either haemorrhage or thromboembolism. Patient factors that affect response to vitamin K include age, body-weight, co-morbidity or health status, warfarin daily dose, and genetic polymorphism. The authors called for a more individualised approach to the reversal of over-anticoagulation.

A study has shown that dietary vitamin K intake is an important factor in anticoagulation instability; even brief periods of increased or decreased intake had significant effects on anticoagulation.[6] A high intake of green, leafy vegetables or selected oil-based foods can readily provide a dietary intake of 500 micrograms of vitamin K. Instead of restricting dietary vitamin K, maintenance of a stable intake may result in improved maintenance of therapeutic anticoagulation.[7]

Concern has also been expressed about possible effects on patients taking warfarin if vitamin K is included in their parenteral nutrition.[8]

1. Welbert RT, *et al.* Correction of excessive anticoagulation with low-dose oral vitamin K_1. *Ann Intern Med* 1997; 125: 959–62.
2. Petrow CW, *et al.* Antagonism of warfarin-induced hypoprothrombinemia with use of low-dose subcutaneous vitamin K_1. *J Clin Pharmacol* 1997; 37: 751–7.
3. Hanslik T, Prinseau J. The use of vitamin K in patients on anticoagulant therapy: a practical guide. *Am J Cardiovasc Drugs* 2004; 4: 43–55.
4. DeZee KJ, *et al.* Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med* 2006; 166: 391–7.
5. Sconce EA, Kamali F. Appraisal of current vitamin K dosing algorithms for the reversal of over-anticoagulation with warfarin: the need for a more tailored dosing regimen. *Eur J Haematol* 2006; 77: 457–62.
6. Franco V, *et al.* Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. *Am J Med* 2004; 116: 651–6.
7. Bovill EG, *et al.* Vitamin K and oral anticoagulation: thought for food. *Am J Med* 2004; 116: 711–13.
8. Bern M. Observations on possible effects of daily vitamin K replacement, especially upon warfarin therapy. *J Parenter Enteral Nutr* 2004; 28: 388–98.

Vitamin K deficiency bleeding. Vitamin K deficiency bleeding (VKDB; haemorrhagic disease of the newborn; HDN), of which 3 types have been recognised, is associated with a clotting defect due to vitamin K deficiency.[1,2]

- In early VKDB bleeding occurs at the time of delivery or during the first 24 hours of life and is typically seen in infants whose mothers have taken drugs that affect vitamin K metabolism such as warfarin, some antiepileptics, rifampicin, or isoniazid.
- Classic VKDB, the most common type, usually occurs at 2 to 5 days of age and breast feeding is an important factor as human breast milk has a much lower content of vitamin K than either cow's milk or infant formulas.
- Late VKDB presents frequently as intracranial haemorrhage in infants over one month of age. The vitamin-K deficiency in these cases can be either idiopathic (usually in breast-fed infants who did not receive vitamin K at birth) and/or can be a secondary manifestation of other disorders such as chronic diarrhoea, cystic fibrosis or other malabsorption syndromes, biliary atresia, or α_1-antitrypsin deficiency.

Treatment of VKDB involves use of intravenous phytomenadione, usually 1 mg initially with further doses depending on response. More immediate treatment, in the form of blood transfusion or blood clotting factors, may be needed to compensate for severe blood loss and delayed response to vitamin K. VKDB, particularly the late type, carries a high risk of morbidity or death; therefore, the emphasis has been on prevention.

It has long been known that giving vitamin K to the neonate soon after birth can reduce the incidence of VKDB. Menadiol sodium phosphate was formerly used, but reports in the 1950s of jaundice and kernicterus in infants given this vitamin K analogue caused concern, and led to the preferential use of phytomenadione either intramuscularly or orally. Giving phytomenadione, has been standard practice for neonates considered at high risk of VKDB, such as those who had a complicated delivery, those born prematurely, and those whose mothers were receiving antiepileptic therapy. Since it is not possible to selectively identify all neonates that are at risk for VKDB, the routine use of phytomenadione in all neonates has been advocated. However, such practice has been controversial, particularly as regards the route.[2-4]

Some consider that oral dosage is less invasive and more acceptable to parents.[4] However, there has also been concern about the adequacy of absorption of oral phytomenadione. In addition, there was some evidence[2,5-7] to suggest that a single intramuscular dose was more effective than a single oral dose in preventing late VKDB, and that repeated oral doses might be required, which may be less convenient and carry the risk of poor compliance. More recently, a possible increased risk of childhood cancer in neonates treated with intramuscular, but not oral, phytomenadione has been reported (see Carcinogenicity, p. 2124.2). Although the association remains controversial, it led to recommendations for the preferential use of oral vitamin K in neonates at low-risk of VKDB in some countries, including the UK[8] and Germany,[9] whereas other countries, including the USA,[10,11] still preferred the intramuscular route for all neonates.

There is still no agreement on the most effective route or dosage regimen, and study of this has been complicated by issues concerning the available formulations. A colloidal, micelle formulation (licensed for oral use in some countries) was introduced to replace the original preparation which contained polyoxyl castor oil, propylene glycol, and phenol (unlicensed for oral use but often given in this way). Although replacing the original formulation has eased concerns about the safety of its excipients, it is not known if the new formulation provides sustained protection when given intramuscularly. Oral absorption of the new formulation has also prompted discussion.[12] A report[13] of the failure of prophylaxis in 3 breast-fed babies (2 of whom had unidentified cholestatic liver disease) who received 2 oral doses of the micellar formulation, as recommended in Switzerland, emphasises the importance of the third, and possibly, other, follow-up doses. Plasma vitamin K concentrations in breast-fed infants receiving 3 oral doses of this formulation were at least equal to concentrations in those receiving a single intramuscular dose.[14] A study in Germany, however, found the micellar oral formulation to be no more efficacious than older vitamin K preparations,[15] and a pharmacokinetic study found its absorption to be unreliable in infants with conjugated hyperbilirubinaemia;[16] the authors suggest that even 3 oral doses may not provide sufficient protection against VKDB in infants with latent cholestasis.

Advice issued in 1998 from the UK Department of Health[17] advocates that all newborn infants should receive vitamin K prophylaxis, both oral and intramuscular routes should be available, and that parents should be involved in the decision on which route is used. In healthy neonates of 36 weeks' gestation or over, licensed product information in the UK recommends a dose of 1 mg phytomenadione as a single intramuscular injection soon after birth. Alternatively, 2 mg may be given orally soon after birth, followed by a second dose of 2 mg at 4 to 7 days; a third oral dose of 2 mg should be given to exclusively breast-fed babies one month after birth. In preterm neonates of less than 36 weeks' gestation, an intramuscular or intravenous dose of 400 micrograms/kg (maximum 1 mg) may be given soon after birth. The *BNFC* states that the intramuscular route should be used in those infants considered to be at particular risk for VKDB, and also suggests that infants with cholestatic disease should be given either intramuscular or intravenous phytomenadione as oral absorption is likely to be impaired. Additionally, subsequent oral doses are suggested for neonates given an initial intravenous dose, in order to provide comparable prolonged protection to the intramuscular route.

Other regimens have been investigated or are in use elsewhere. One hospital in the USA has satisfactorily used, for many years, a single 2-mg dose given via nasogastric tube to neonates after birth,[18] although the American Academy of Pediatrics still advocates use of the intramuscular route.[11] In Denmark, a 2-mg oral or intramuscular dose at birth followed by a weekly oral dose of 1 mg during the first 3 months of life has effectively prevented any late VKDB in healthy breast-fed babies.[19] In the Netherlands a lower dose regimen of 1 mg orally or intramuscularly at birth, followed by 25 micrograms daily or 1 mg weekly by mouth from 1 week to 3 months of age has been found satisfactory.[20] However, a retrospective comparison of dose regimens used in Denmark and the Netherlands revealed that the lower doses used in the Netherlands did not provide protection against VKDB in breast-fed infants with unrecognised cholestasis due to biliary atresia.[21] In France, for formula-fed neonates at no risk of haemorrhage, 2 mg is given orally at birth, followed by a second dose between day 2 and 7; infants who are breast-fed are given weekly oral doses of 2 mg until

cessation of exclusive breast feeding. For neonates at high risk of haemorrhage, however, the first dose is given intramuscularly, or even by slow intravenous injection, according to the clinical state of the infant.[2]

Although phytomenadione crosses the placenta slowly and to a limited extent, it is nevertheless recommended that pregnant women receiving drugs that are vitamin K antagonists (particularly antiepileptics) should receive phytomenadione 10 to 20 mg daily from 36 weeks of gestation.[2,22] This is in addition to the requirement that their neonates, who are at high risk of VKDB, receive intramuscular phytomenadione soon after birth. Maternal phytomenadione has been investigated as a means of improving vitamin K status in breast-fed neonates. In 1 study,[23] 5 mg daily for 12 weeks was effective for this purpose.

1. Hathaway WE. Haemostatic disorders in the newborn. In: Bloom AL, Thomas DP, eds. *Haemostasis and thrombosis*. 2nd ed. Edinburgh: Churchill Livingstone,1987: 554–69.
2. Autret-Leca E, Jonville-Béra A-P. Vitamin K in neonates: how to administer, when and to whom. *Paediatr Drugs* 2001; 3: 1–8.
3. Tripp JH, McNinch AW. Haemorrhagic disease and vitamin K. *Arch Dis Child* 1987; 62: 436–7.
4. Brown SG, *et al.* Should intramuscular vitamin K prophylaxis for haemorrhagic disease of the newborn be continued? A decision analysis. *N Z Med J* 1989; 102: 3–5.
5. Clarkson PM, James AG. Parenteral vitamin K_1: the effective prophylaxis against haemorrhagic disease for all newborn infants. *N Z Med J* 1990; 103: 95–6.
6. McNinch AW, Tripp JH. Haemorrhagic disease of the newborn in the British Isles: two year prospective study. *BMJ* 1991; 303: 1105–9.
7. Von Kries R. Neonatal vitamin K. *BMJ* 1991; 303: 1083–4.
8. British Paediatric Association. *Vitamin K prophylaxis in infancy*. London, 1992: British Paediatric Association.
9. von Kries R, *et al.* Repeated oral vitamin K prophylaxis in West Germany: acceptance and efficacy. *BMJ* 1995; 310: 1097–8.
10. American Academy of Pediatrics Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993; 91: 1001–3.
11. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. *Pediatrics* 2003; 112: 191–2.
12. Clarke P, Shearer MJ. Vitamin K deficiency bleeding: the readiness is all. *Arch Dis Child* 2007; 92: 741–3.
13. Baenziger O, *et al.* Oral vitamin K prophylaxis for newborn infants: safe enough? *Lancet* 1996; 348: 1456.
14. Greer FR, *et al.* A new mixed micellar preparation for oral vitamin K prophylaxis: randomised controlled comparison with an intramuscular formulation in breast fed infants. *Arch Dis Child* 1998; 79: 300–5.
15. von Kries R, *et al.* Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F109–F112.
16. Pereira SP, *et al.* Intestinal absorption of mixed micellar phylloquinone (vitamin K_1) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F113–F118.
17. Department of Health. *Vitamin K for newborn babies*. London, 1998: Department of Health. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Professionalletters/Chiefmedicalofficerletters/DH_4004993?IdcService=GET_FILE&dID=76345Rendition=Web (accessed 21/07/08)
18. Clark PI, James EJP. Twenty-seven years of experience with oral vitamin K_1 therapy in neonates. *J Pediatr* 1995; 127: 301–4.
19. Nørgaard Hansen K, Ebbesen F. Neonatal vitamin K prophylaxis in Denmark: three years' experience with oral administration during the first three months of life compared with one oral administration at birth. *Acta Paediatr Scand* 1996; 85: 1137–9.
20. Cornelissen M, Hirasing R. Vitamin K for neonates. *BMJ* 1994; 309: 1441–2.
21. van Hasselt PM, *et al.* Netherlands Study Group for Biliary Atresia Registry. Prevention of vitamin K deficiency bleeding in breastfed infants: lessons from the Dutch and Danish biliary atresia registries. *Pediatrics* 2008; 121: e857–e863.
22. Delgado-Escueta AV, Janz D. Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. *Neurology* 1992; 42 (suppl 5): 149–60.
23. Greer FR, *et al.* Improving the vitamin K status of breastfeeding infants with maternal vitamin K supplements. *Pediatrics* 1997; 99: 88–92.

Adverse Effects and Precautions

Intravenous doses of *phytomenadione* have caused severe reactions resembling hypersensitivity or anaphylaxis. Symptoms have included facial flushing, sweating, chest constriction and chest pain, dyspnoea, cyanosis, and cardiovascular collapse; fatalities have been reported. Anaphylactic reactions have generally been associated with an overly rapid rate of infusion but have also been reported even when the solution was diluted and infused slowly. They are generally thought to be due to polyoxyl castor oil which is present as a surfactant in some parenteral formulations; reports of such reactions with formulations that do not contain polyoxyl castor oil are rare (but see Hypersensitivity, below).

Pain, swelling, and phlebitis may occur at the injection site when phytomenadione is given. Localised skin reactions including atrophy or necrosis have been reported after intramuscular or subcutaneous injection of phytomenadione.

Phytomenadione formulations solubilised with lecithin and a bile salt should be given with caution to patients with severely impaired liver function and to premature neonates weighing less than 2.5 kg, since the bile salt may displace bilirubin.

Giving *menadione* and *menadiol sodium phosphate* to neonates, especially premature infants, or to the mother during late pregnancy has been associated with the development in the infant of haemolytic anaemia, hyperbilirubinaemia, and kernicterus, and such use is not recommended. Phytomenadione has a lower risk of haemolysis. Menadione and menadiol sodium phosphate have also been reported to cause haemolysis in patients with G6PD deficiency or vitamin E deficiency.

Breast feeding. Vitamin K is variably distributed into breast milk; a study found phytomenadione concentrations in the first 10 mL of expressed milk ("fore milk") to be lower than those in the last 10 mL ("hind milk"). These changes may be related to the lipid concentration, which is higher in hind milk. Lipid composition also changes over the course of lactation, with pronounced changes in the first week, and the authors proposed that a mechanism exists whereby vitamin K concentration in milk is higher in the first few days of life so as to meet the neonate's nutritional requirements at a time when vitamin K status is precarious.[1] The American Academy of Pediatrics considers[2] that, as no adverse effects have been seen in breast-fed infants whose mothers were receiving phytomenadione, its use is therefore usually compatible with breast feeding.

1. von Kries R, *et al.* Vitamin K_1 content of maternal milk: influence of the stage of lactation, lipid composition, and vitamin K_1 supplements given to the mother. *Pediatr Res* 1987; 22: 513–17.
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 09/01/06)

Carcinogenicity. A case-control study from the UK[1] suggested an increased risk of cancer in children who had received vitamin K at birth for the prevention of vitamin K deficiency bleeding (see p. 2123.2). A further study[2] by the same authors indicated that this risk was associated with intramuscular, but not oral, dosage, and was strongest for childhood leukaemia. In response to these data, the British Paediatric Association recommended that the oral route should be preferred for prophylaxis,[3] whereas the American Academy of Pediatrics continued to advocate the intramuscular route,[4] and still does so, concluding there is no association between this route and childhood leukaemia or other cancers.[5]

Subsequent studies from the USA,[6] Sweden,[7] Denmark,[7,8] Germany,[9] and England[10] did not confirm an increased risk of childhood cancer, including leukaemias, after the use of intramuscular vitamin K. Subsequently 4 further studies were published.[11-14] Two of these, a case-control study in Scotland[11] and an ecological study in Britain,[12] showed no increased risk of any cancers with the use of intramuscular vitamin K. A third case-control study in England and Wales[13] found a borderline association between intramuscular vitamin K and cancers, particularly leukaemia. In the fourth study, a case-control study in northern England,[14] there was an increased risk (odds ratio 1.79) of acute lymphoblastic leukaemia developing 1 to 6 years after birth in children who had received intramuscular vitamin K. In 1998 a review[15] by an expert working group of the UK CSM concluded that there was no increased risk of solid tumours with vitamin K, and that, although an increased risk of leukaemia could not be excluded, observed results were compatible with chance. Moreover, they could not identify a plausible mechanism for a carcinogenic effect of vitamin K. Since then, a pooled analysis of case-control studies in Great Britain and Germany[16] found no convincing evidence that vitamin K given intramuscularly was associated with childhood leukaemia. A national case-control study in the UK[17] concluded there was no evidence that vitamin K, irrespective of the route, influenced the risk of children developing leukaemia or any other cancer. If there is any increased risk, it is likely to manifest only in a very small subpopulation who are at high risk for some as-yet-unidentified biological reason.[18] The UK Department of Health[19] advocates either oral or intramuscular prophylaxis, and recommends that the parents should be involved in the decision on which route is used.

1. Golding J, *et al.* Factors associated with childhood cancer in a national cohort study. *Br J Cancer* 1990; 62: 304–8.
2. Golding J, *et al.* Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992; 305: 341–6.
3. British Paediatric Association. *Vitamin K prophylaxis in infancy*. London, 1992: British Paediatric Association.
4. American Academy of Pediatrics Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993; 91: 1001–3.
5. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. *Pediatrics* 2003; 112: 191–2. [Re-affirmed May 2006]
6. Klebanoff MA, *et al.* The risk of childhood cancer after neonatal exposure to vitamin K. *N Engl J Med* 1993; 329: 905–8.
7. Ekelund H, *et al.* Administration of vitamin K to newborn infants and childhood cancer. *BMJ* 1993; 307: 89–91.
8. Olsen JH, *et al.* Vitamin K regimens and incidence of childhood cancer in Denmark. *BMJ* 1994; 308: 895–6.
9. von Kries R, *et al.* Vitamin K and childhood cancer: a population based case-control study in Lower Saxony, Germany. *BMJ* 1996; 313: 199–203.
10. Ansell P, *et al.* Childhood leukaemia and intramuscular vitamin K: findings from a case-control study. *BMJ* 1996; 313: 204–5.
11. McKinney PA, *et al.* Case-control study of childhood leukaemia and cancer in Scotland: findings for neonatal intramuscular vitamin K. *BMJ* 1998; 316: 173–7.
12. Passmore SJ, *et al.* Ecological studies of relation between hospital policies on neonatal vitamin K administration and subsequent occurrence of childhood cancer. *BMJ* 1998; 316: 184–9.
13. Passmore SJ, *et al.* Case-control studies of relation between childhood cancer and neonatal vitamin K administration. *BMJ* 1998; 316: 178–184
14. Parker L, *et al.* Neonatal vitamin K administration and childhood cancer in the north of England: retrospective case-control study. *BMJ* 1998 316: 189–93.
15. CSM/MCA. Safety of intramuscular vitamin K (Konakion). *Current Problems* 1998; 24: 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023236&RevisionSelectionMethod=LatestReleased (accessed 21/07/08)
16. Roman E, *et al.* Vitamin K and childhood cancer: analysis of individual patient data from six case-control studies. *Br J Cancer* 2002; 86: 63–9.
17. Fear NT, *et al.* Vitamin K and childhood cancer: a report from the United Kingdom Childhood Cancer Study. *Br J Cancer* 2003; 89: 1228–31.
18. Ross JA, Davies SM. Vitamin K prophylaxis and childhood cancer. *Med Pediatr Oncol* 2000; 34: 434–7.
19. DoH. *Vitamin K for newborn babies*. London, 1998: Department of Health. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Professionalletters/Chiefmedicalofficerletters/DH_4004993?IdcService=GET_FILE&dID=76345Rendition=Web (accessed 21/07/08)

Effects on the blood. Cerebral arterial thrombosis developed in 2 patients with malabsorption syndromes due to coeliac disease during treatment with vitamin K for severe deficiency of vitamin-K-dependent coagulation factors. An increased tendency to thrombotic events had previously been reported to be present in patients with intestinal inflammatory disorders. It was suggested that if bleeding did occur in such patients treatment should be with plasma infusions or small doses of vitamin K but that vitamin K deficiency should not be specifically treated since a gluten-free diet or corticosteroids given for the gastrointestinal disorder will result in a gradual correction.[1]

1. Florholmen J, *et al.* Cerebral thrombosis in two patients with malabsorption syndrome treated with vitamin K. *BMJ* 1980; 281: 541.

Hypersensitivity. Hypersensitivity reactions have been reported after subcutaneous,[1-3] intramuscular,[4] intravenous,[5-7] and oral[7] use of vitamin K, although the incidence is low.[6,7]

Subcutaneous doses are considered to pose less risk of **anaphylaxis** than the intravenous route;[5] fatalities have been reported with intravenous use,[7] even after low doses given slowly, and by dilute infusion.[5,7] There has also been a fatality associated with oral use.[7] While anaphylactoid reactions have been attributed to the polyoxyl castor oil vehicle,[6,7] a direct immune mechanism has also been proposed.[7]

Vitamin K itself appears to be the antigen causing adverse **cutaneous reactions**.[3] Two types of cutaneous reaction have been described: pruritic, erythematous, eczematous plaques usually occurring up to 2 weeks after a dose, and sclerodermoid morphea-like plaques, with or without eczema, which may be delayed.[1,3,4] In addition, there have been rare reports of diffuse maculopapular eruption, but the relationship of this reaction to vitamin K use has been questioned.[3] Despite reports that the eczematous reactions resolve faster than the sclerodermatous reactions, persistent eczema[4] or pruritus has occurred.[3]

Treatment has been largely symptomatic: topical and systemic corticosteroids and antihistamines have been used.[1,3,4] For patients who have previously reacted to phytomenadione injections, the use of menadione either by injection or by mouth has been suggested;[3] cross-reactivity was not anticipated to be a problem. However, cross-reactions on patch testing have been reported.[4] It has been suggested that reactions to vitamin K in patients might signify underlying hepatic disease,[1] although others believe the condition is seen more frequently in patients with liver disease since they are often those requiring vitamin K.[3]

1. Gettler SL, Pung MA. Indurated plaques on the arms of a 52-year-old man. *Arch Dermatol* 2001; 137: 957–62.
2. Bui L, *et al.* Skin reaction to subcutaneous phytonadione injections. *Am J Health-Syst Pharm* 2004; 61: 407.
3. Wilkins K, *et al.* Cutaneous reactions associated with vitamin K_1. *J Cutan Med Surg* 2000; 4: 163–7.
4. Sommer S, *et al.* Type IV hypersensitivity to vitamin K. *Contact Dermatitis* 2002; 46: 94–6.
5. Wjasow C, McNamara R. Anaphylaxis after low dose intravenous vitamin K. *J Emerg Med* 2003; 24: 169–72.
6. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K_1): a 5-year retrospective review. *Ann Allergy Asthma Immunol* 2002; 89: 400–406.
7. Fiore LD, *et al.* Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis* 2001; 11: 175–83.

Overdosage. UK licensed product information states that, while there is no known clinical syndrome attributable to hypervitaminosis of phytomenadione, adverse effects have been reported after overdose in neonates and infants. These include jaundice, hyperbilirubinaemia, increases in liver enzyme values, abdominal pain, constipation, soft stools, malaise, agitation, and skin eruptions. Most adverse events were not considered to be serious, and resolved without any treatment.

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Vitamin K decreases the effects of oral anticoagulants (see p. 1535.3), and is used to counteract excessive effects of these drugs, see Uses and Administration, p. 2122.3. Vitamin K may reduce the response to resumed therapy with anticoagulants for a week or more.

Pharmacokinetics

The fat-soluble vitamin K compounds phytomenadione and menadione require the presence of bile for their absorption from the gastrointestinal tract; the water-soluble derivatives can be absorbed in the absence of bile. Vitamin K accumulates mainly in the liver but is stored in the body only for short periods of time. Vitamin K does not appear to cross the placenta readily and it is variably distributed into breast milk. Phytomenadione is rapidly metabolised to more polar metabolites and is excreted in bile and urine as glucuronide and sulfate conjugates.

Absorption. Absorption of phytomenadione from the colloidal (micellar) preparation was more irregular and unpredictable after intramuscular than intravenous dosage in healthy adults;[1] when used as an antidote to anticoagulant, this formulation should be given intravenously. In neonates, plasma phytomenadione concentrations were within or above the adult fasting plasma range 24 days after receiving a single dose of the colloidal preparation either orally (3 mg) or intramuscularly (1.5 mg).[2]

1. Soedirman JR, *et al.* Pharmacokinetics and tolerance of intravenous and intramuscular phylloquinone (vitamin K_1) mixed micelles formulation. *Br J Clin Pharmacol* 1996; 41: 517–23.
2. Schubiger G, *et al.* Vitamin K_1 concentration in breast-fed neonates after oral or intramuscular administration of a single dose of a new mixed-micellar preparation of phylloquinone. *J Pediatr Gastroenterol Nutr* 1993; 16: 435–9.

Human Requirements

The minimum daily requirements of vitamin K are not clearly defined but an intake of about 1 microgram/kg daily appears to be adequate. Vitamin K requirements in normal adults can be met from the average diet and from the synthesis of menaquinones (also known as vitamin K_2) by bacterial action in the intestine. Vitamin K occurs naturally as phytomenadione (vitamin K_1), which is present in many foods, especially leafy green vegetables such as cabbage and spinach, and is also present in avocado, meat, cow's milk, egg-yolk, and some cereals.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p. 2046.1) has been set for vitamin K although an intake of 1 microgram/kg daily was considered to be both safe and adequate for adults; a higher intake of 10 micrograms daily (about 2 micrograms/kg daily) was believed to be justified in infants because of the absence of hepatic menaquinones in early life and reliance on dietary vitamin K alone. It was stated that all babies should receive prophylactic vitamin K at birth[1] and for further details concerning neonatal use, see Vitamin K Deficiency Bleeding, p. 2123.2.

In the USA, adequate intake levels have been determined to be 120 micrograms daily for adult men and 90 micrograms daily for adult women.[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 vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: K1; Konakion; Mestil-Ka; Rupek; *Austral.*: Konakion; PM Ausphyllo; *Austria*: Konakion; *Belg.*: Konakion; Vitamon K; *Braz.*: Kanakion; Kavit; Menadion; Vikatron; Vita K; *Chile*: Auriderm K2†; Konakion; *China*: Glakay (固力康); Kai Nai Jin (凯乃金); *Cz.*: Kanavit; *Denm.*: Konakion; Menadion; *Fin.*: Konakion; *Ger.*: Ka-vit; Kanavit†; Konakion; *Gr.*: Kapavit; Konakion; *Hong Kong*: Auriderm†; Konakion; Uni-Menadol†; Univitan K1; *Hung.*: Konakion; *India*: Injek; K-Nat; Kapilin; Kenadion; KVI; *Indon.*: Neo-K; *Irl.*: Konakion; *Israel*: Konakion; *Ital.*: Konakion; Vita K Plus; *Jpn*: Glakay; Kaytwo; Kaywan; *Malaysia*: Kisan; Konakion; *Mex.*: Danapril; Dionadion; K-50; Konakion†; Royken; *Neth.*: Konakion; *Norw.*: Konakion; *NZ*: K-Thrombin†; Konakion; *Philipp.*: Clotigen†; Cycomin; Hema-K; Hemadone; Hemo-K†; Kona-K; Konakion; Vitakay; *Pol.*: Vitacon; *Port.*: Kanakion; *S. Afr.*: Konakion; *Singapore*: Konakion; *Spain*: Kaergona Hidrosoluble†; Konakion; *Swed.*: Konakion; *Switz.*: Konakion; *Thai.*: Glakay; Konakion; KP; *Turk.*: Konakion MM; Libavit K; Vi-Plex K; *UK*: Konakion; Neokay; *USA*: Mephyton.

Multi-ingredient Preparations. *Arg.*: Aderogyl; Estreptocarbocaftiazol; Estreptocarbocaftiazol; Kacerutin; *Austral.*: Bone Matrix Support; Nutribone; OsteoEze Bone & Joint; PM Kiddiecal; PM NextG Cal; Vitalipid N; *Austria*: Vitalipid; *Belg.*: Vitalipid; *Chile*: Hepabil; K-Gel; Katin; Microret K†; Vitalipid N; *China*: Vitalipid N (维他利匹特); Zhi Wei Bao (知维保); *Cz.*: Vitalipid N; *Denm.*: Vitalipid; *Fin.*: Vitalipid; *Fr.*: Vitalipide; *Ger.*: Vitalipid; *Gr.*: Vitalipid; *Hong Kong*: Vitalipid N; *Hung.*: Vitalipid; *India*: Cadisper C; CKP†; Gynae-CVP; Gystat; Kalpastic†; Siochrome; Styptocid; Styptocip; *Indon.*: Biocal-95; Cal-95; Calciviton; Calplex; Calvitos; Hi-Bone; Ossovit Plus; Ossovit; Phoscal; Steopor; Vitalipid N; *Irl.*: Bio-Calcium + D_3 + K†; Vitlipid N; *Israel*: Vitalipid N; *Ital.*: 3Mil; Dicovit DK; Ditrevit K; Nadione; Vitalipid; *Malaysia*: Vitalipid N†; *Mex.*: Anadekin†; Hemosin-K; Microka†; Microret K; *Neth.*: Vitintra; *Norw.*: Vitalipid; *NZ*: Vitalipid; *Pol.*: Vitalipid N; *Port.*: Vitalipid; *Rus.*: Vectrum Calcium (Вектрум Кальций); Vitalipid N (Виталипид Н); *S.Afr.*: Vitalipid; *Singapore*: Vitalipid N; *Spain*: Vitalipid; *Swed.*: Vitalipid; *Switz.*: Vitalipid N; *Thai.*: Bio-Calcium + D_3 + K; Siduol; Vitalipid; *Turk.*: Vitalipid N; *UK*: Vitlipid N; *Ukr.*: Osteoartisi Max (Остеоартизи Макс); *USA*: OstiGen; REQ49+; TheraCal D; Viactiv Calcium†.

Pharmacopoeial Preparations

BP 2014: Menadiol Phosphate Injection; Menadiol Phosphate Tablets; Phytomenadione Injection; Phytomenadione Tablets;

USP 36: Menadiol Sodium Diphosphate Injection; Menadiol Sodium Diphosphate Tablets; Menadione Injection; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-soluble Vitamins Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Phytonadione Injectable Emulsion; Phytonadione Tablets.

Whey

Milk Plasma; Milk Serum.

CAS — 92129-90-3 (whey protein).

UNII — 8617ZSFMF6.

Profile

Whey is the liquid remaining after milk has curdled or been strained. It contains lactose, proteins, vitamins, and minerals and has been used as a nutritional supplement. It has also been used in skin-care products. Commercially it is used as a source of lactose and lactic acid.

Reviews.

1. Marshall K. Therapeutic applications of whey protein. *Altern Med Rev* 2004; 9: 136–56.
2. Yalçin AS. Emerging therapeutic potential of whey proteins and peptides. *Curr Pharm Des* 2006; 12: 1637–43.
3. Krissansen GW. Emerging health properties of whey proteins and their clinical implications. *J Am Coll Nutr* 2007; 26: 713S–723S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bio-Prot; *Indon.*: Dermylex; *Ital.*: Balsamo Primi Denti.

Multi-ingredient Preparations. *Arg.*: Lactacyd; *Austral.*: Hommer; *Chile*: Lactacyd; *China*: Lactacyd (乐特喜); *Hong Kong*: Lactacyd; *India*: Kiddis; *Indon.*: Lactacyd; *Ital.*: Lactacyd Derma; Lactacyd Intimo; *Malaysia*: Lactacyd; *Philipp.*: Lactacyd; *Singapore*: Lactacyd; *Thai.*: Lactacyd†.

Dried Yeast

Brewers' Yeast; Cerevisiae Fermentum Siccatum; Faex Siccata; Fermento de Cerveja; Levadura desecada; Levedura Sêca; Levure de Bière; Saccharomyces Siccum; Trockenhefe; Сушёные Дрожжи.

Pharmacopoeias. In *Jpn*.

Profile

Dried yeast consists of unicellular fungi belonging to the family Saccharomycetaceae, dried by a process that avoids decomposition of the vitamins present. The chief species are *Saccharomyces cerevisiae, S. carlsbergensis,* and *S. monacensis.* Dried yeast contains thiamine, nicotinic acid, riboflavin, pyridoxine, pantothenic acid, biotin, folic acid, cyanocobalamin, aminobenzoic acid, inositol, and chromium.

Dried yeast is a rich source of vitamins of the B group. It has been used for the prevention and treatment of vitamin B deficiency in oral doses of 1 to 8 g daily.

Yeast may be enriched by growing it in the presence of various minerals. Chromium-enriched yeast (chromium yeast), iron-enriched yeast (iron yeast), selenium-enriched yeast (selenium yeast), and zinc-enriched yeast (zinc yeast) have been used as dietary supplements.

Yeast is an ingredient of some preparations for treating haemorrhoids, and some preparations intended to restore normal gastrointestinal flora (see Probiotics, p. 2596.3). Yeast is widely used in brewing.

Antibiotic-associated colitis. Although other organisms, including *Candida* spp., have been implicated in antibiotic-associated diarrhoea, colonisation of the colon with *Clostridium difficile*, a toxin-producing Gram-positive anaerobe, is the most common identifiable cause of antibiotic-associated colitis (p. 183.1) and pseudomembranous colitis. There are reports of benefit with dried yeast in patients with *C. difficile*-associated diarrhoea;[1,2] commercially available brewers' yeast tablets were used, at a dose of 3 tablets three times daily (strength unspecified), in 3 patients refractory to standard treatment,[1] or as adjunctive therapy in 11 patients, using the same dose.[2]

1. Schellenberg D, *et al.* Treatment of Clostridium difficile diarrhoea with brewer's yeast. *Lancet* 1994; 343: 171–2.
2. Barthram J, *et al.* Further research warranted. *Pharm J* 1997; 259: 371.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Levedo†; *Canad.*: Action O G†; *China*: Ebios (爱菲斯); Fu Xi Kang (富希康); Xi Wei Er (西维尔); *Denm.*: SelenoPrecise; *Fr.*: Chromasvelt†; *Ger.*: Eubiol; Hamadin N; Hefekapseln†; Omniflora Akut†; Perocur†; Peromyces†; Santax S†; Yomogi; *Hung.*: Bio-Strath; *India*: Laviest†; *Indon.*: Bio-Strath; *Ital.*: Zimocel; *Mex.*: Levifusa; *Pol.*: Ceroselt; *Rus.*: Vitanam (Витанам); *Switz.*: Sanaflor; *Thai.*: Brewers Yeast; *UK*: Bio-Strath; *Ukr.*: Micerol (Мицерол)†.

Multi-ingredient Preparations. *Arg.*: Bifena; Indian Health - Levadura; Karbonetas†; RNA DNA; Tonovital Plus Antioxidante; Totalflora; Tricomax; *Austral.*: Cold & Flu Relief; Hair Skin & Nails; *Austria*: Aktivanad; Levurinetten†; Sperti Preparation H; *Braz.*: Leveglutan; Pantogar; *Canad.*: Floradix Kindervital†; Floradix Tab†; Kyolic 101†; Multi Enzyme†; Nervrite; Optibiol†; Preparation H; Right Choice AM†; Ultra-Vit Plus†; *Chile*: Biogenol; Cellvital†; Sperti Preparation H; *Cz.*: Merz Special†; Preparation H; Revalid; *Fr.*: Actisoufre; Alpharegul Femme; Calciforte Vitamin D_3; Calciforte†; Calciforte; Carbolevure; Forcical Vitamine D3†; Levure Or†; Notrinot†; Phytophanere†; Selenium-ACE†; Solacy; Spasmag; Tranquilimag†; *Ger.*: Aktivanad-N; Dia-Aktivanad-N; Eulatin NH; Pantovigar; *Gr.*: Preparation H; *Hong Kong*: Merz Special†; Pantogar; Revicon; *Hung.*: Epasel; Metabol; Revalid; Sperti Preparation H; Szelen +C; *India*: Apenic; Cypon; Eliferri; Genozyme; Hapeast; Medithane; Miproten; Plastules B-12; *Indon.*: Bio-Strath; Lycoxy; Maxivit; Oxypen; Pantogar; ProBi; Yeastafort; *Irl.*: Preparation H†; *Israel*: Preparation H; *Ital.*: Biomineral 5-Alfa; Carfosid; Eu-Visus; Eurogel; Florelax; Lactisporin; Lactivis; Lactolife; Lactovit; Lievitosohn; Lievitovit; Preparazione H; Vigogel; Vitreolux; *Malaysia*: Evelle; Revicon; Seresis; *Mex.*: Seresis; *Neth.*: Sperti Preparation H; *Philipp.*: Lungcaire Plus; Nutricap; Nutrigrow†; Revicon Forte (Improved); Thinber Fiber Complex†; *Pol.*: Vegevit B_{12}; *Port.*: Sperti Preparacao H; *Rus.*: Antioxycaps with Selenium (Антиоксикапс С Селеном); Doppelherz Selevit (Доппельгерц Селевит)†; Pantovigar (Пантовигар); Preparation H (Препарейшн Эйч)†; *S.Afr.*: Preparation H†; Selenium-ACE; Vitaforce Nutri-B†; *Singapore*: Bios Life; Evelle; Pantogar; Preparation H; Revicon; Seresis†; Vitaton; *Spain*: Preparacion H†; *Switz.*: Carbolevure; Merz Dragees Specialest†; Pantogar; Revalid†; Sperti Preparation H†; Strath Gouttes contre la toux; Strath Gouttes pour l'estomac; Strath Gouttes pour le foie et la bile; Strath Gouttes pour le nerfs et contre l'insomnie; Strath Gouttes pour les muqueuses; Strath Gouttes pour les reins et la vessie; *Thai.*: Convits; Polybee; Revicon†; *Turk.*: Pantogar; *UK*: Bio-Strath Artichoke Formula; Bio-Strath Valerian Formula; Bio-Strath Willow Formula; Brewers Yeast; Preparation H; Se-Power; Tonic Yeast; Travelbac; Yeast Vite; *Ukr.*: Fitoval Capsules (Фитовал капсулы); OxyLic (ОксиЛик); Pantogar (Пантогар); Revalid (Ревалид); Vitrum Cardio (Витрум Кардио); *USA*: Preparation H; Rectagene Medicated Balm; Wyanoids Relief Factor; *Venez.*: Nutricap; Optibiol; Selene; Uvagen; Vitalux.

Zeaxanthin

Anchovyxanthin; E161(h); Zeaxanthol; Зеаксантин.

(3*R*,3′*R*)-β,β-Carotene-3,3′-diol.

$C_{40}H_{56}O_2$=568.9

CAS — 144-68-3.

UNII — CV0IB81ORO.

Pharmacopoeias. *US* has *meso*-zeaxanthin.

USP 36: (*meso*-Zeaxanthin). *meso*-Zeaxanthin consists chiefly of the 3*R*,3′*S*-isomer of zeaxanthin. It contains not less than 80.0% of total carotenoids calculated as zeaxanthin and not less than 74.0% of zeaxanthin, calculated with reference to the anhydrous drug. Store in airtight containers. Protect from light.

Profile

Zeaxanthin is a naturally occurring carotenoid that is promoted as a dietary supplement for age-related macular degeneration (p. 880.2).

References.

1. Mares-Perlman JA, *et al.* The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease: overview. *J Nutr* 2002; 132 (suppl): 518S–524S.
2. Mozaffarieh M, *et al.* The role of the carotenoids, lutein and zeaxanthin, in protecting against age-related macular degeneration: a review based on controversial evidence. *Nutr J* 2003; 2: 20.
3. Hartmann D, *et al.* Plasma kinetics of zeaxanthin and 3'-dehydro-lutein after multiple oral doses of synthetic zeaxanthin. *Am J Clin Nutr* 2004; 79: 410–17.
4. Thumham DI, *et al.* A supplementation study in human subjects with a combination of meso-zeaxanthin, (3R,3'R)-zeaxanthin and (3R,3'R,6'R)-lutein. *Br J Nutr* 2008; 100: 1307–14.
5. Zeimer M, *et al.* Kurz- und mittelfristige Anderungen der makulären Pigmentdichte infolge der Supplementation mit Lutein und Zeaxanthin sowie Koantioxidanzien: die LUNA-Studie. *Ophthalmologe* 2009; 106: 29–36.
6. Roberts RL, *et al.* Lutein and zeaxanthin in eye and skin health. *Clin Dermatol* 2009; 27: 195–201.
7. Stringham JM, *et al.* The influence of dietary lutein and zeaxanthin on visual performance. *J Food Sci* 2010; 75: R24–R29.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Lutein-Vision Advanced; *Canad.*: ICaps Lutein and Zeaxanthin; Visionex; *Chile*: Vision Tabs; *Fr.*: Difravision; Lero Pervulane; Macula; PreserVision; Sun Vue; Trioptec; Visioprev; *Hong Kong*: Ocuvite; Visionex†; *India*: GV-24; I-Lute; I-Site; Lutivit; Lycocare; Lycofact Plus; Ocufree; Ocugold; Oxy-V; *Indon.*: Ervision; Eyebright; Eyevit; Kapset; Lubire; Lutevit; Matoflam; Matovit AX; Matovit Fifty; nutrivision; Nuvision; Optimax Plus; Proview; Retivit Plus; Retop; *Irl.*: Ocuvite†; *Ital.*: Astar; Connivea; Euretin Duo; Macvit; Meralut; Troca Vit; VisuQ10; Zeadema Crono; Zeadema; *Malaysia*: Eurobio Bio-Vizmax; *Mex.*: Drusen; Icaps; Optivision; Snelvit; *Philipp.*: Nutricap; *Rus.*: Complivit Oftalmo (Компливит Офтальмо); *Singapore*: I-Vitein; Icaps; Nutrivision†; Ocuvite Adult 50+; Optibiol; Visionex†; *Thai.*: Ocuvite; *UK*: Icaps; *Ukr.*: Ocuvite Complete (Окювайт Комплит); Ocuvite Lutein Forte (Окювайт Лютеин форте); Oko-Health (Око-хелс); Optix (Оптикс); Optix Forte (Оптикс Форте); Vitrum Foreyes (Витрум Форайз); Vitrum Foreyes Forte (Витрум Форайз Форте); *USA*: Cardio Tone; Clinical Nutrients 50-Plus Men; Fitness Tabs for Men; Fitness Tabs for Women; MacuTrition; Ocuvite Eye + Multi; Preservision Eye Vitamin; REQ49+; *Venez.*: Vilox; Vitavision.

Zinc

Cynk; Zincum; Zink; Цинк.

Zn=65.38

CAS — 7440-66-6.

UNII — J41CSQ7QDS (zinc); 13S1S8SF37 (zinc ion).

Zinc Acetate

Cink-acetát-dihidrát; Cinko acetatas dihidratas; Cynku octan; E650; Octan zinečnatý dihydrát; Sinkkiasetaatti; Zinc (acétate de) dihydraté; Zinc acetato de; Zinci Acetas; Zinci Acetas Dihydricus; Zinkacetat; Ацетат Цинка; Уксуснокислый Цинк.

$(CH_3CO_2)_2Zn,2H_2O$=219.5

CAS — 557-34-6 (anhydrous zinc acetate); 5970-45-6 (zinc acetate dihydrate).

ATC — A16AX05.

ATC Vet — QA16AX05.

UNII — FM5526K07A (zinc acetate dihydrate); H2ZEY72PME (anhydrous zinc acetate).

NOTE. Zinc Acetate, Basic is *rINN*.

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

Ph. Eur. 8: (Zinc Acetate Dihydrate; Zinc Acetate BP 2014). A white or almost white, crystalline powder or leaflets. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 5.8 to 7.0. Store in nonmetallic containers.

USP 36: (Zinc Acetate). White crystals or granules having a slight acetous odour. Is slightly efflorescent. Soluble 1 in 2.5 of water and 1 in 30 of alcohol; freely soluble in boiling alcohol. pH of a 5% solution in water is between 6.0 and 8.0. Store in airtight containers.

Zinc Chloride

Chlorid zinečnatý; Cink-klorid; Cinko chloridas; Cynku chlorek; Sinkkikloridi; Zinc, chlorure de; Zinc, cloruro de; Zinci chloridum; Zincum Chloratum; Zinkchlorid; Zinkklorid; Хлористый Цинк; Цинка Хлорид.

$ZnCl_2$=136.3

CAS — 7646-85-7.

ATC — B05XA12.

ATC Vet — QB05XA12.

UNII — 86Q357L16B.

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

Ph. Eur. 8: (Zinc Chloride). A white or almost white, deliquescent, crystalline powder or cast in white or almost white sticks. Very soluble in water; freely soluble in alcohol and in glycerol. An approximately 10% solution in water has a pH of 4.6 to 5.5. Store in nonmetallic containers.

USP 36: (Zinc Chloride). A white or practically white, odourless, crystalline powder, or white or practically white crystalline granules. May also be in porcelain-like masses or moulded into cylinders. It is very deliquescent. Soluble 1 in 0.5 of water, 1 in 1.5 of alcohol, and 1 in 2 of glycerol. Its solution in water or in alcohol is usually slightly turbid, but the turbidity disappears when a small quantity of hydrochloric acid is added. A 10% solution in water is acid to litmus. Store in airtight containers.

Turbidity. Zinc chloride almost always contains some oxychloride which produces a slightly turbid aqueous solution. Turbid solutions, except when intended for ophthalmic use, may be cleared by adding gradually a small amount of dilute hydrochloric acid. Solutions of zinc chloride should be filtered through asbestos or sintered glass, since they dissolve paper and cotton wool.

Zinc Citrate

Zinc Citrate Trihydrate; Цитрат Цинка.

2-Hydroxy-1,2,3-propanetricarboxylic acid zinc salt.

$C_{12}H_{10}O_{14}Zn_3,3H_2O$=628.4

CAS — 546-46-3.

UNII — K72I3DEX98 (anhydrous zinc citrate); GNM26GAX7R (zinc citrate trihydrate).

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

USP 36: (Zinc Citrate).

Zinc Gluconate

Zinc, gluconate de; Zinc, gluconato de; Zinci gluconas; Zinkgluconat; Цинка Глюконат.

$C_{12}H_{22}O_{14}Zn$=455.7

CAS — 4468-02-4.

ATC — A12CB02.

ATC Vet — QA12CB02.

UNII — U6WSN5SQ1Z.

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

Ph. Eur. 8: (Zinc Gluconate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; practically insoluble in absolute alcohol and in dichloromethane. Store in non-metallic, airtight containers.

USP 36: (Zinc Gluconate). White or practically white powder or granules. Soluble in water; very slightly soluble in alcohol. pH of a 1% solution in water is between 5.5 and 7.5.

Zinc Lactate

Zinc Dilactate; Zinc Sarcolactate (*S*-isomer).

$C_6H_{10}O_6Zn$=243.5

CAS — 554-05-2; 16039-53-5.

UNII — 2GXR25858Y.

Zinc Sulfate

Zinc, sulfato de; Çinko Sülfat; Cinko sulfatas; Cink-szulfát; Cynku siarczan; Sinkkisulfaatti; Siran zinečnatý; Zinc, sulfate de; Zinc Sulphate; Zinci sulfas; Zincum Sulfuricum; Zinksulfat; Сернокислый Цинк; Цинка Сульфат.

$ZnSO_4,7H_2O$=287.5

CAS — 7733-02-0 (anhydrous zinc sulfate); 7446-20-0 (zinc sulfate heptahydrate).

ATC — A12CB01.

ATC Vet — QA12CB01.

UNII — 89DS0H96TB (zinc sulfate); 0J6Z13X3WO (anhydrous zinc sulfate); PTX099XSF1 (zinc sulfate monohydrate); N5ZI12K7MP (zinc sulfate heptahydrate).

NOTE. 'White vitriol' or 'white copperas' is crude zinc sulfate.

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

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

Eur. also includes the monohydrate and the hexahydrate.

US includes the monohydrate and the heptahydrate in one monograph.

Ph. Eur. 8: (Zinc Sulfate Heptahydrate; Zinci Sulfas Heptahydricus). Colourless, transparent, crystals or a white or almost white, crystalline powder; efflorescent. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic airtight containers.

Ph. Eur. 8: (Zinc Sulfate Hexahydrate; Zinci Sulfas Hexahydricus). Colourless, transparent, crystals or a white or almost white, crystalline powder; efflorescent. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic airtight containers.

Ph. Eur. 8: (Zinc Sulfate Monohydrate; Zinci Sulfas Monohydricus). Colourless, transparent, crystals or a white or almost white crystalline powder. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.0 to 5.6. Store in nonmetallic containers.

USP 36: (Zinc Sulfate). It contains one or seven molecules of water of hydration. Colourless, transparent, prisms, or small needles. May occur as a white, granular, crystalline powder. It is odourless and is efflorescent in dry air. Very soluble in water (heptahydrate); freely soluble in water (monohydrate); practically insoluble in alcohol (monohydrate) insoluble in alcohol (heptahydrate); freely soluble in glycerol (heptahydrate). Its solutions are acid to litmus. Store in airtight containers.

Uses and Administration

Zinc is an essential element of nutrition and traces are present in a wide range of foods. It is a constituent of many enzyme systems and is present in all tissues. Features of zinc deficiency include growth retardation and defects of rapidly-dividing tissues such as the skin, the immune system, and the intestinal mucosa. Water-soluble zinc salts are used as supplements to correct zinc deficiency; for example, in malabsorption syndromes, during parenteral feeding, in conditions with increased body losses (trauma, burns, and protein-losing states), and in acrodermatitis enteropathica (a rare genetic disorder characterised by severe zinc deficiency). They have been tried in the treatment of a large number of conditions that may be related to zinc deficiency.

Doses of zinc salts are usually expressed in terms of elemental zinc, and the following salts contain about 50 mg of zinc:

- zinc acetate (dihydrate) 168 mg
- zinc chloride 104 mg
- zinc citrate (trihydrate) 160 mg
- zinc gluconate 348 mg
- zinc lactate 186 mg
- zinc sulfate (heptahydrate) 220 mg

The approximate number of millimoles of zinc contained in these salts are:

- 4.6 mmol in 1 g zinc acetate (dihydrate)
- 7.3 mmol in 1 g zinc chloride
- 4.8 mmol in 1 g zinc citrate (trihydrate)
- 2.2 mmol in 1 g zinc gluconate
- 4.1 mmol in 1 g zinc lactate
- 3.5 mmol in 1 g zinc sulfate (heptahydrate)

In deficiency states, zinc is usually given orally as the sulfate, the sulfate monohydrate, or the gluconate, in doses of up to 50 mg of elemental zinc three times daily. When intravenous supplements are required, zinc chloride or zinc sulfate may be given; a suggested dose for parenteral nutrition is 6.5 mg of elemental zinc (100 micromoles) daily.

Oral zinc salts, commonly the acetate, may be used as copper absorption inhibitors in **Wilson's disease** (p. 1567.3). The usual adult dose is 50 mg three times daily up to a maximum of five times daily. An effective dose in pregnant women is usually 25 mg three times daily; however, dosage is adjusted based on copper concentrations.

For doses in children, see Administration in Children, below and Diarrhoea, under Deficiency States, p. 2127.2.

Zinc sulfate is used topically in a variety of skin conditions mainly for its **astringent** properties. The insoluble zinc salts, commonly the oxide (p. 1729.1), are used similarly. A 1.2% solution of zinc acetate is used topically with erythromycin in the treatment of acne vulgaris (p. 1682.2). Zinc sulfate is also used as an astringent in eye drops. Zinc chloride has been used for its powerful caustic and astringent properties, usually in very dilute solution, in, for example, mouthwashes. Zinc citrate and zinc lactate are used in preparations for oral care and as a dietary supplement.

Polaprezinc (p. 1879.1) is also used as a source of zinc.

Homoeopathy

Zinc and its salts have been used in homoeopathic medicines.

Administration in children. Zinc can be given to children to prevent and treat deficiency or as a copper absorption inhibitor in Wilson's disease (p. 1567.3). The following doses are expressed as elemental zinc.

In **deficiency states**, zinc can be given orally according to weight:

- less than 10 kg, 22.5 mg daily
- 10 to 30 kg, 22.5 mg once to three times daily
- over 30 kg, 45 mg once to three times daily

The *BNFC* suggests an oral dose of zinc 1 mg/kg daily for neonates.

When intravenous supplements are required, suggested doses of zinc for children vary between countries. UK licensed product information recommends a dose of 250 micrograms/kg (up to a maximum of 3.75 mg) daily for children weighing 40 kg or less; children weighing more than 40 kg should receive the adult dose (see p. 2126.3). In the USA, licensed product information recommends a dose of 300 micrograms/kg daily for preterm neonates weighing up to 3 kg, and 100 micrograms/kg daily for full term infants and children up to 5 years. Adult doses may be used in older children.

In **Wilson's disease**, zinc is given orally according to age:

- 1 to 6 years, 25 mg twice daily
- 6 to 16 years and body-weight under 57 kg, 25 mg three times daily
- over 16 years or body-weight above 57 kg, 50 mg three times daily

For **acrodermatitis enteropathica**, the *BNFC* suggests an initial oral dose of zinc 0.5 to 1 mg/kg twice daily for all ages (the total daily dose may alternatively be given in 3 divided doses).

For oral zinc doses recommended in the management of acute diarrhoea in children, see below. Zinc sulfate may also be applied topically, see Uses and Administration p. 2126.3.

Age-related macular degeneration. High doses of dietary supplements such as betacarotene, vitamin C, vitamin E, and zinc are being promoted for preservation of vision in the elderly but there are no data to suggest any benefit for patients who do not have age-related macular degeneration or have only mild disease and such treatment is not necessarily harmless.[1] For further details, see under Betacarotene, p. 2051.2.

1. Anonymous. Antioxidant vitamins and zinc for macular degeneration. *Med Lett Drugs Ther* 2003; 45: 45–46.

Common cold. Zinc salts have been tried (orally or intranasally) in the treatment of the common cold (p. 951.1) with variable results.[1-9] A systematic review of randomised studies (conducted in upper-middle and high-income countries, where zinc deficiency is uncommon) found that oral zinc reduced the duration and severity of common cold symptoms when used therapeutically, and that it reduced the incidence of the common cold in healthy children when used prophylactically. However, no firm recommendations could be made regarding the dose, formulation, and duration that should be used.[10]

1. Mossad SB, *et al.* Zinc gluconate lozenges for treating the common cold: a randomized, double-blind, placebo-controlled study. *Ann Intern Med* 1996; 125: 81–8.
2. Macknin ML, *et al.* Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. *JAMA* 1998; 279: 1962–7.
3. Prasad AS, *et al.* Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; 133: 245–52.
4. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis* 2000; 31: 1202–8.
5. Eby GA. Zinc lozenges as cure for the common cold—a review and hypothesis. *Med Hypotheses* 2010; 74: 482–92.
6. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. *Clin Infect Dis* 2001; 33: 1865–70.
7. Hirt M, *et al.* Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. *Ear Nose Throat J* 2000; 79: 778–82.
8. Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. *Q J Med* 2003; 96: 35–43.
9. Belongia EA, *et al.* A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *Am J Med* 2001; 111: 103–8.
10. Singh M, Das RR. Zinc for the common cold. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 20/10/11).

Deficiency states. General references.

1. Bambidge M. Human zinc deficiency. *J Nutr* 2000; 130 (suppl): 1344S–1349S.
2. Prasad AS. Zinc deficiency: has been known of for 40 years but ignored by global health organisations. *BMJ* 2003; 326: 409–10.
3. Shrimpton R, *et al.* Zinc deficiency: what are the most appropriate interventions? *BMJ* 2005; 330: 347–9.
4. Mason P. Physiological and medicinal zinc. *Pharm J* 2006; 276: 271–4.

DIAGNOSIS AND TESTING. A loss of taste acuity is a sign of zinc deficiency (see Taste Disorders, below) and this has been used as a test for the condition: patients who do not immediately perceive a strong flavour on tasting a dilute (typically 0.1 or 0.2%) solution of zinc sulfate are considered likely to benefit from supplementation. However, a study in pregnant women failed to confirm that the ability to taste such a solution was related to zinc deficiency.[1]

Authors of a small study of Japanese children with short stature evaluated body zinc clearance, and considered those patients with high clearance values but normal serum zinc concentrations to have marginal zinc deficiency.[2]

1. Mahomed K, *et al.* Failure to taste zinc sulphate solution does not predict zinc deficiency in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1993; 48: 169–75.
2. Kaji M, *et al.* Studies to determine the usefulness of the zinc clearance test to diagnose marginal zinc deficiency and the effects of oral zinc supplementation for short children. *J Am Coll Nutr* 1998; 17: 388–91.

DIARRHOEA. Chronic diarrhoea can be a sign of zinc deficiency, and diarrhoea can lead to excessive zinc losses and zinc deficiency when dietary zinc is inadequate. Zinc supplements have been shown to reduce the incidence, intensity, or duration of acute diarrhoea (p. 1805.2) in children in developing countries.[1-5] Beneficial effects have also been seen with zinc supplementation for persistent diarrhoea.[4,5] A WHO report concluded that zinc supplementation is efficacious in significantly reducing the severity and duration of diarrhoea; the type of zinc salt does not appear to influence efficacy, although the best formulation should be determined to minimise adverse effects such as vomiting.[6] A further report[7] concluded that there was sufficient evidence to recommend the inclusion of zinc as adjunctive therapy to oral rehydration salts in the standard management of both dysenteric and non-dysenteric acute diarrhoea. WHO guidelines on the management of acute diarrhoea recommend 10 to 14 days of oral zinc supplementation at a dose of 10 mg daily for infants under 6 months of age, and 20 mg daily for older children.[8] It has been suggested that HIV-infected children should also receive zinc supplementation for diarrhoea, see HIV infection and AIDS, below.

For a report of increased efficacy in reducing persistent diarrhoea and dysentery when zinc is used with vitamin A, see Diarrhoea, under Deficiency states, p. 2100.1. For suggestions that zinc potentiates the effect of vitamin A, see Vitamin A deficiency, below.

1. Bhutta ZA, *et al.* Zinc Investigators' Collaborative Group. Prevention of diarrhea and pooled analysis of randomized controlled trials. *J Pediatr* 1999; 135: 689–97.
2. Bhutta ZA, *et al.* Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr* 2000; 72: 1516–22.
3. Aggarwal R, *et al.* Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. *Pediatrics* 2007; 119: 1120–30.
4. Fischer Walker CL, Black RE. Micronutrients and diarrheal disease. *Clin Infect Dis* 2007; 45 (suppl 1): S73–S77.
5. Lukacik M, *et al.* A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrhea. *Pediatrics* 2008; 121: 326–36.
6. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea. *J Health Popul Nutr* 2001; 19: 338–46.
7. Robberstad B, *et al.* Cost-effectiveness of zinc as adjunct therapy for acute childhood diarrhoea in developing countries. *Bull WHO* 2004; 82: 523–31.
8. WHO/UNICEF. WHO/UNICEF joint statement: clinical management of acute diarrhoea (issued May 2004). Available at: http://www.afro.who.int/en/tanzania/tanzania-publications/doc_download/617-acute-diarrhoea-joint-statement.html (accessed 22/07/10)

GROWTH RETARDATION. Growth retardation in a group of short Japanese children without endocrine abnormalities was found to be associated with mild to moderate zinc deficiency; supplementation with oral zinc sulfate 5 mg/kg daily over 6 months resulted in an improvement in growth velocity despite unchanged growth hormone production.[1] Similarly, supplementation with 10 mg zinc daily for 6 days of each week, for 6 months, increased the growth rate of stunted Ethiopian infants; weight also increased in both stunted and non-stunted children, and the authors commented that these effects were at least partly due to improvements in appetite, and reduced morbidity from infection.[2] Results from a meta-analysis of these 2 studies and 31 others indicated that zinc supplementation resulted in a highly significant increase in both linear growth and weight gain of prepubertal children; weight-for-height index was not affected. Significant increases in serum zinc concentrations were also noted with supplementation, but additional studies were considered necessary in order to determine whether mean serum zinc concentration could accurately predict response to supplementation.[3]

1. Nakamura T, *et al.* Mild to moderate zinc deficiency in short children: effect of zinc supplementation on linear growth velocity. *J Pediatr* 1993; 123: 65–9.
2. Umeta M, *et al.* Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial. *Lancet* 2000; 355: 2021–6.
3. Brown KH, *et al.* Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2002; 75: 1062–71.

HIV INFECTION AND AIDS. A systematic review[1] found that zinc supplements reduced diarrhoeal morbidity in HIV-infected children in a single study, without causing adverse effects on disease progression; it was considered that children with HIV should receive zinc supplements in the management of diarrhoea (p. 1805.2) or severe malnutrition in the same way as uninfected children.

1. Irlam JH, *et al.* Micronutrient supplementation in children and adults with HIV infection. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 22/12/10).

PNEUMONIA. A pooled analysis[1] of 10 studies performed in developing countries found that zinc supplementation reduced the incidence of pneumonia in children by 41%. A randomised study in Bangladesh, in 270 children aged 2 to 23 months, found that 20 mg daily of elemental zinc, given orally and adjuvant to standard antimicrobial therapy, accelerated recovery from pneumonia when compared with placebo; children aged 12 months or older resolved their respiratory illness earlier than younger infants.[2] Another study in Bangladesh,[3] involving 1621 children 2 to 12 months old, found that prophylaxis with 70 mg of oral zinc acetate [about 20 mg of zinc] given weekly reduced the incidence of pneumonia compared with placebo and also reduced subsequent pneumonia-related mortality; a small reduction in the incidence of diarrhoea was also seen.

However, a later systematic review[4] including 15 randomised controlled studies concluded that on balance the evidence suggested no additional benefit of oral zinc supplementation in children with community-acquired pneumonia who were receiving antimicrobial therapy; there was also no evidence of benefit in preventing pneumonia, and one study had suggested a possible increased incidence and prevalence in children given the supplement.

1. Bhutta ZA, *et al.* Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. *J Pediatr* 1999; 135: 689–97.
2. Brooks WA, *et al.* Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. *Lancet* 2004; 363: 1683–8.
3. Brooks WA, *et al.* Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. *Lancet* 2005; 366: 999–1004.
4. Mathew JL. Zinc supplementation for prevention or treatment of childhood pneumonia: a systematic review of randomized controlled trials. *Indian Pediatr* 2010; 47: 61–6.

PREGNANCY. Zinc requirements are increased in pregnancy. Although it is unclear to what extent this has clinical consequences, some have suggested that supplementation with modest doses of zinc (less than 45 mg daily) during pregnancy may have beneficial effects on fetal growth and development, and lead to improved pregnancy outcomes.[1] A controlled study in Peru found that addition of oral zinc (25 mg of zinc daily as zinc sulfate) to iron and folate supplementation improved fetal bone growth, as measured by femur length.[2] A systematic review[3] concluded that, while zinc supplementation during pregnancy appears to reduce preterm delivery, there was no convincing evidence that it resulted in other useful benefits. Since the association with preterm birth might reflect poor nutrition, improvement in the overall nutritional status of impoverished populations would be more beneficial than zinc supplementation in isolation.

1. Favier M, Hininger-Favier I. Zinc et grossesse. *Gynecol Obstet Fertil* 2005; 33: 253–8.
2. Merialdi M, *et al.* Randomized controlled trial of prenatal zinc supplementation and fetal bone growth. *Am J Clin Nutr* 2004; 79: 826–30.
3. Mahomed K, *et al.* Zinc supplementation for improving pregnancy and infant outcome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 05/03/08).

TASTE DISORDERS. Zinc appears to be effective for the treatment of taste disturbances (p. 1047.2) associated with zinc deficiency but there is insufficient evidence to determine its efficacy for taste dysfunction secondary to conditions that do not involve low serum zinc concentrations.[1] Zinc picolinate was found to significantly improve objective measurement of taste when compared with placebo, both in patients with zinc deficiency and in those with idiopathic taste disorders (and normal serum zinc concentrations); there were no differences in subjective assessment of taste.[2] A later study[3] also found oral zinc gluconate 140 mg daily [about 20 mg of zinc] to be of benefit in idiopathic dysgeusia. In contrast, loss of taste has been reported in some patients using zinc gluconate intranasally, see p. 2128.1.

Polaprezinc (p. 1879.1) is also being investigated as a treatment for taste disorders.

1. Heyneman CA. Zinc deficiency and taste disorders. *Ann Pharmacother* 1996; 30: 186–7.
2. Sakai F, *et al.* Double-blind, placebo-controlled trial of zinc picolinate for taste disorders. *Acta Otolaryngol* 2002; (suppl 546): 129–33.
3. Heckmann SM, *et al.* Zinc gluconate in the treatment of dysgeusia—a randomized clinical trial. *J Dent Res* 2005; 84: 35–8. Correction. *Ibid.*: 382.

Vitamin A deficiency. It has been proposed[1] that the inconsistent effects on morbidity of vitamin A supplementation (see Diarrhoea, under Deficiency States, p. 2100.1) may be due to co-existing micronutrient deficiencies, such as zinc deficiency, that affect the bioavailability of vitamin A. The authors found combined zinc and vitamin A supplementation to be more effective in reducing persistent diarrhoea and dysentery than either zinc or vitamin A alone. There is also some suggestion that zinc may potentiate the effects of vitamin A in the treatment of night blindness,[2] but only in those patients already deficient in zinc. A study in Bangladesh[3] found that the proportional improvement in vitamin A status in vitamin A-deficient children was larger in those given zinc with vitamin A than in those given vitamin A or zinc alone, suggesting a synergistic effect. Similarly, a study in Indonesia[4] of supplementation in pregnant women found that betacarotene with zinc, but not betacarotene or zinc alone, improved vitamin A status in both mothers and infants at 6 months postpartum; the authors suggested that zinc

may have a specific role in the conversion of betacarotene to retinol.

1. Rahman MM, *et al.* Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001; 323: 314–18.
2. Christian P, *et al.* Zinc supplementation might potentiate the effect of vitamin A in restoring night vision in pregnant Nepalese women. *Am J Clin Nutr* 2001; 73: 1045–51.
3. Rahman MM, *et al.* Synergistic effect of zinc and vitamin A on the biochemical indexes of vitamin A nutrition in children. *Am J Clin Nutr* 2002; 75: 92–8.
4. Dijkhuizen MA, *et al.* Zinc plus β -carotene supplementation of pregnant women is superior to β -carotene supplementation alone in improving vitamin A status in both mothers and infants. *Am J Clin Nutr* 2004; 80: 1299–1307.

Wilson's disease. References.

1. Anderson LA, *et al.* Zinc acetate treatment in Wilson's disease. *Ann Pharmacother* 1998; 32: 78–87.
2. Brewer GJ, *et al.* Treatment of Wilson's disease with zinc XV long-term follow-up studies. *J Lab Clin Med* 1998; 132: 264–78.
3. Brewer GJ, *et al.* Treatment of Wilson's disease with zinc XVII: treatment during pregnancy. *Hepatology* 2000; 31: 364–70.
4. Brewer GJ. Zinc acetate for the treatment of Wilson's disease. *Expert Opin Pharmacother* 2001; 2: 1473–7.

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of zinc salts (the gluconate and sulfate) given orally are gastrointestinal and include abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, and gastritis. These are particularly common if zinc salts are taken on an empty stomach, and may be reduced by giving them with meals.

In acute overdosage zinc salts are corrosive, due to the formation of zinc chloride by stomach acid; treatment consists of giving milk or alkali carbonates and activated charcoal. The use of emetics or gastric lavage should be avoided.

Prolonged use of high doses of zinc supplements, orally or parenterally, leads to copper deficiency with associated sideroblastic anaemia and neutropenia; full blood counts and serum cholesterol should be monitored to detect early signs of copper deficiency. Zinc toxicity has occurred after the use of contaminated water in haemodialysis solutions. High serum zinc concentrations may be reduced by using a chelating drug such as sodium calcium edetate (p. 1573.2).

Metal fume fever is an occupational disease associated with inhalation of freshly-oxidised metal fumes, most commonly from zinc, iron or copper. It is characterised by chills, fever, cough, dyspnoea, myalgia, and chest pain, and is generally self-limiting and does not appear to be associated with long-term sequelae.

Effects on the blood. There have been reports[1-3] of anaemia, leucopenia, and neutropenia in patients consuming excessive amounts of zinc supplements for acne. A patient given zinc-containing enteral feeds as well as zinc supplementation was diagnosed with sideroblastic anaemia due to zinc toxicity.[4] All patients were copper-deficient,[1-4] despite supplementation with copper in one case.[4]

1. Porea TJ, *et al.* Zinc-induced anemia and neutropenia in an adolescent. *J Pediatr* 2000; 136: 688–90.
2. Igic PG, *et al.* Toxic effects associated with consumption of zinc. *Mayo Clin Proc* 2002; 77: 713–16.
3. Salzman MB, *et al.* Excessive oral zinc supplementation. *J Pediatr Hematol Oncol* 2002; 24: 582–4.
4. Irving JA, *et al.* Element of caution: a case of reversible cytopenias associated with excessive zinc supplementation. *Can Med Assoc J* 2003; 169: 129–31.

Effects on the senses. The FDA's adverse event reporting system received 131 reports of anosmia (loss of the sense of smell) associated with the use of intranasal zinc-containing preparations (Zicam).[1] These products contained zinc gluconate, were marketed in the USA from 1999 to June 2008, and were used to prevent and treat cold symptoms, usually for about 3 days. Loss of smell was often associated with an initial burning sensation in the nose, and occurred soon after intranasal use; anosmia was long-lasting or permanent in most cases. Loss of taste was also reported in some patients.

1. FDA. Zinc-containing intranasal cold products (marketed as Zicam) and anosmia. *FDA Drug Safety Newsletter* 2009; 2: 26–7. Also available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/UCM192395.pdf (accessed 04/02/10)

Hypersensitivity. Report of a patient who developed palmoplantar pustulosis about 1 year after receiving dental fillings containing zinc.[1] Zinc hypersensitivity was confirmed by *in vitro* and patch testing. Complete remission occurred on replacing the dental fillings.

1. Yanagi T, *et al.* Zinc dental fillings and palmoplantar pustulosis. *Lancet* 2005; 366: 1050.

Parenteral nutrition. Zinc was found to be a common contaminant of various components used for TPN, and rubber stoppers or glass may have been the source.[1] Levels of zinc found may exceed daily requirements even before the addition of supplementary zinc. The authors suggested it may be important to routinely monitor zinc status in patients receiving long-term TPN, particularly infants and children.

1. Bak EB, *et al.* Chromium and zinc contamination of parenteral nutrient solution components commonly used in infants and children. *Am J Health-Syst Pharm* 1998; 55: 150–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zinc 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 07/10/11)

Interactions

The absorption of zinc may be reduced by iron supplements (see also Absorption, under Pharmacokinetics, below), penicillamine, phosphorus-containing preparations, and tetracyclines. Zinc supplements reduce the absorption of copper, fluoroquinolones (see Antacids and Metal Ions, under Interactions of Ciprofloxacin, p. 265.1), iron, penicillamine, and tetracyclines (p. 375.3).

Pharmacokinetics

Absorption of zinc from the gastrointestinal tract is incomplete, and is reduced in the presence of some dietary constituents such as phytates. Bioavailability of dietary zinc varies widely between different sources, but is about 20 to 30%. Zinc is distributed throughout the body with the highest concentrations found in muscle, bone, skin, eye, and prostatic fluids. It is primarily excreted in the faeces, and regulation of faecal losses is important in zinc homoeostasis. Small amounts are lost in urine and perspiration.

Absorption. Although zinc deficiency (see Deficiency States, under Uses and Administration, p. 2127.1) in some cases may be due to inadequate dietary intake, inhibitors of zinc absorption may also be causative.[1] *Phytates*, which are present in cereals, corn, legumes, and rice, inhibit zinc absorption. The animal *protein* in beef, eggs, and cheese counteracts the inhibitory effect of phytate, whereas the casein in milk decreases zinc absorption. Proteins also often contain other constituents such as inorganic *phosphate* that can negatively affect zinc absorption. Long-term use of *calcium* supplements has no effect on zinc status, but dietary calcium may form insoluble complexes with phytate and zinc, thus decreasing the absorption of zinc. *Iron* can reduce zinc absorption, although the effect is apparent only at a very high ratio of iron to zinc, and in aqueous solution, which suggests that iron fortification of foods will not affect zinc absorption. Although it is possible that iron supplementation could affect mechanisms of zinc uptake and transport, studies have not found such an effect, and long-term iron supplementation is not considered to impair zinc status.

Zinc can form complexes with ligands or chelators; if the complex is readily absorbed, this can increase zinc absorption. *Edetic acid* has been found to have variable effects on zinc status depending on the ratio of edetic acid to other cations and phytate, which compete for complex formation with zinc. *Histidine* also chelates with zinc and can increase plasma zinc concentrations; however, the ratio of histidine to zinc is important because high doses of histidine may enhance the urinary excretion of zinc. *Methionine* may improve zinc absorption, although evidence is limited. Adding organic acids such as *citrate* to foods can enhance zinc absorption; zinc citrate has been used as a dietary supplement.

1. Lönnerdal B. Dietary factors influencing zinc absorption. *J Nutr* 2000; 130: 1378S–1383S.

Human Requirements

UK and US recommended dietary intake. In the UK dietary reference values (DRV)[1] and in the USA recommended dietary allowances (RDA)[2] (see Human Requirements, p. 2046.1) have been published for zinc. In the UK the reference nutrient intake (RNI) for adult males and females is 9.5 and 7.0 mg daily respectively; values are also given for infants and children of varying ages and for lactating women. The Expert Group on Vitamins and Minerals[3] have established a safe upper level (SUL) for zinc of 25 mg daily. In the USA the RDA for adults is 11 mg daily for men and 8 mg daily for women.[2] The tolerable upper intake level is 40 mg daily.

WHO recommend lower limits of the safe ranges of population mean intakes of dietary zinc for 3 categories of diets based on high, moderate, and low zinc bioavailability: values are 4.0, 6.5, and 13.1 mg dietary zinc daily for women, and 5.6, 9.4, and 18.7 mg dietary zinc daily for men, respectively.[4] They recommend an upper limit of the safe range of population mean intakes of zinc of 35 mg daily for women, and 45 mg daily for men.

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 vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 14/11/05)
4. WHO. Zinc. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 72–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Galzin; *Austral.*: Zincaps; *Austria*: Wilzin; *Belg.*: Wilzin; *Braz.*: Dermezil; Zincopan; *Canad.*: Anusol; Anuzinc†; Bio Statol; Egozinc; Flavo-Zinc†; Men Formula†; Micro Zn; Rivasol; Shaklee DR; *Chile*: Altazinc; Cleanance; Num-Zit; *China*: Likexin (利可欣); Ping An (屏安); Wei Er (威尔); Xing Rui Ling (星瑞灵); *Cz.*: Wilzin; Zincteral†; Zinkorotat-POS†; *Denm.*: BiOrto Zink; Wilzin; *Fr.*: Effizinc; Rubozinc; Suboligo Zinc†; Wilzin†; *Ger.*: Biolectra Zink; Cefazink; Curazink; Nefro-Zinc†; Ophtal Z†; Ophtopur-Z†; Tussamag Zink†; Unizink; Virudermin; Vitazink; Wilzin; Zink AL; Zink beta; Zink Hexal†; Zink Verla; Zink-D Longoral; Zink-Injekt N; Zink-Ratiopharm; Zink-Sandoz†; Zinkaspart; Zinkbrause; Zinkit; Zinkorot; Zinkotase; *Gr.*: Solvazinc; Wilzin; *Hong Kong*: Anuzinc†; Egozinc†; Eye Glo Relief; Zincaps; *Hung.*: Feroglobin-B12; *India*: Adrovit-Z; Aquasol Ceezed; Ascazin; Gludel; Infladase Forte; Keeper; *Indon.*: Interzinc; Orezinc; Zidiar; Zincare; Zincpro; Zn-Diar; *Irl.*: Solvazinc†; Wilzin; *Israel*: Avazinc; Micro Zn; Zincol; *Ital.*: Pontefix; Wilzin; *Mex.*: Unguento del Bebe; Z-Crim†; *Neth.*: Wilzin; *Norw.*: Solvezink; Wilzin; *NZ*: Zincaps; *Philipp.*: E-Zinc; Immuzinc; Lipactin; Nutrizinc; Orazinc; Prozinc; Zinbee; *Pol.*: Wilzin; Zincas; Zincteral; *Port.*: Wilzin; *Rus.*: Zincteral (Цинктерал); *Spain*: Wilzin; *Swed.*: Solvezink; Wilzin; *Switz.*: Collazin; Virudermin; Zink Verla; *Thai.*: Z-G; Zinc Tab; Zincaps; Zincate; Zinctab; *Turk.*: Medizinc; Nutri-Zinc; Zinco; Zincobest; Zincover; Zinvital; *UK*: Flavo-Zinc; Solvazinc; Tartar Control Listerine; Wilzin; Zincomed; Zincosol; *Ukr.*: Zincteral (Цинктерал); Zinkit (Цинкит); *USA*: Dermadrox; Galzin; Halls Zinc Defense; Ivy Dry; Orazinc; PeleVerus Clear; Verazinc; Zinca-Pak†; Zincate; *Venez.*: Cicalfate.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. *Austral.*: Nervatona Calm; Nervatona Focus; Snore Eze; *Austria*: Gracil; *Canad.*: Cold Tablets with Zinc†; Echinacea Compositum; Formula PC 223†; Weight Loss Kit†; *Chile*: Ikoplex No 9; *Cz.*: Vita C-R15 forte†; Vita C-R15†; *Fr.*: Abbe Chaupitre no 23†; Acidum Phosphoricum Complexe No 5; *Ger.*: Dormi-cyl L Ho-Len-Complex; Gelsemium Comp; Infi-China; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; Phonix Silybum spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; Presselin Nervenkomplex; Presselin Nervennahrung N†; Ranocalcin HM; Rufebran regeno†; Zerosorin SN†; Zincum Hevert N; Zinkokehl; Zinkorell; *Neth.*: Emvita 15; *Rus.*: Passidorm (Пассидорм).

Pharmacopoeial Preparations

BP 2014: Erythromycin and Zinc Acetate Lotion; Zinc Sulphate Capsules; Zinc Sulphate Eye Drops; Zinc Sulphate Injection; Zinc Sulphate Lotion; Zinc Sulphate Tablets;

USP 36: Calcium and Vitamin D with Minerals Tablets; Minerals Capsules; Minerals Tablets; 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; Zinc Acetate Oral Solution; Zinc and Vitamin C Lozenges; Zinc Chloride Injection; Zinc Citrate Tablets; Zinc Gluconate Tablets; Zinc Sulfate Injection; Zinc Sulfate Ophthalmic Solution; Zinc Sulfate Oral Solution; Zinc Sulfate Tablets; Zinc Sulfide Topical Suspension.

Obstetric Drugs

Obstetric Drug Groups, p. 2129
- Ergot alkaloids, p. 2129
- Oxytocics, p. 2129
- Prostaglandins, p. 2129
- Tocolytics, p. 2129

Management of Obstetric Conditions, p. 2129
- Labour induction and augmentation, p. 2129
- Lactation inhibition and induction, p. 2130
- Postpartum haemorrhage, p. 2130
- Premature labour, p. 2131
- Termination of pregnancy, p. 2131

This chapter includes drugs used in obstetrics for the management of labour and postpartum haemorrhage, including various prostaglandins, oxytocics, ergot alkaloids, and tocolytics. Some of these drugs have also been used to terminate pregnancy, as has the antiprogestogen mifepristone (p. 2138.1).

Other drugs with important roles in obstetric management to be found elsewhere in *Martindale* include local anaesthetics (p. 1976.1), opioid analgesics (p. 108.1), and medical gases such as oxygen (p. 1799.3) and nitrous oxide (p. 1908.1). For drugs used in the management of perinatal bacterial infection, see Antibacterials (p. 168.1).

Obstetric Drug Groups

Ergot alkaloids

Some ergot alkaloids have a powerful action on the uterus, causing uterine contractions that are utilised in the active management of the third stage of labour, and to prevent or treat postpartum and postabortal haemorrhage.

Described in this chapter are

Ergometrine, p. 2136.2
Ergot, p. 2137.1
Ergotoxine, p. 2137.2
Methylergometrine, p. 2137.3

Oxytocics

Oxytocics cause contraction of the uterus and may be used for the induction and augmentation of labour, in the management of the third stage of labour, and to prevent and treat postpartum haemorrhage.

Described in this chapter are

Carbetocin, p. 2132.3
Demoxytocin, p. 2133.3
Oxytocin, p. 2143.1

Prostaglandins

Some prostaglandins soften and dilate the cervix and induce contraction of the uterus. They may be used in labour induction, termination of pregnancy, and the treatment of postpartum haemorrhage.

Described in this chapter are

Carboprost, p. 2133.1
Dinoprost, p. 2133.3
Dinoprostone, p. 2134.1
Gemeprost, p. 2137.2
Misoprostol, p. 2140.3
Sulprostone, p. 2145.3

Tocolytics

Tocolytics inhibit uterine contractions and are used in premature labour to delay early delivery. Beta agonists other than ritodrine have also been used, and details on salbutamol (p. 1220.2) and terbutaline (p. 1228.1) can be found in the chapter on Bronchodilators and Anti-asthma Drugs. Other drugs that have been tried for their tocolytic actions include calcium-channel blockers (see Nifedipine, p. 1447.2), glyceryl trinitrate (p. 1391.2), magnesium sulfate (p. 1787.3), and NSAIDs (see Indometacin, p. 71.2).

Described in this chapter are

Atosiban, p. 2132.2
Ritodrine, p. 2145.1

Management of Obstetric Conditions

The management of some obstetric conditions is discussed below.

Labour induction and augmentation

The uterus is normally spontaneously contractile but during pregnancy various physiological mechanisms maintain it in a quiescent state; retention of the fetus is also aided by a firm and contracted cervix. During the final 4 to 5 weeks of pregnancy the cervix normally undergoes a 'ripening' process in which it becomes softened and dilated, so that at parturition it is not a barrier to delivery of the fetus. Endogenous prostaglandins play an important role in this process, and also sensitise the uterus in preparation for labour.

- Labour usually begins spontaneously but in some cases it may be necessary to induce labour, for example in pregnancies that go beyond term or where rupture of the membranes occurs without labour. In other cases there may be indications for early delivery such as maternal hypertensive states, antepartum haemorrhage, intra-amniotic infection (chorioamnionitis), or intra-uterine fetal death.[1,2]
- Once labour has started, augmentation of uterine activity may be necessary if contractions fail to progress satisfactorily. A process of active management of labour, including early oxytocin augmentation, has been used in nulliparous women with a single fetus presenting head-first at term and showing no evidence of fetal compromise. Although it may shorten labour without increasing maternal or neonatal harm, it has not been shown to reduce the rate of caesarean section.[3]

Various techniques are available for **induction of labour**, and the choice may be influenced by the ripeness of the cervix and whether the membranes are intact or have ruptured. Mechanical methods are commonly used and may be all that is needed to induce labour. UK guidelines suggest that sweeping of the membranes (manually separating the lower membrane portion from the uterine wall during vaginal examination) should be offered to women at term.[4] It increases the likelihood of spontaneous labour within 48 hours or birth within one week, and reduces the frequency of formal induction of labour.[5] However, it may cause maternal discomfort, irregular contractions, and bleeding. Laminaria tents, hygroscopic cervical dilators, or Foley (balloon) catheters may be used to stimulate cervical ripening.[1] Although some consider the Foley catheter to be an effective alternative to pharmacological induction with prostaglandins,[6,7] others do not recommend these mechanical methods for routine use in labour induction.[4] Such mechanical methods used for cervical ripening might also increase the risk of maternal and neonatal infection, compared with pharmacological induction.[8] Amniotomy (deliberate rupture of the membranes and release of amniotic fluid) may also be used to stimulate labour, once the cervix becomes favourable.[2] When pharmacological induction of labour is required, a prostaglandin or oxytocin is generally used. WHO[6] recommends oxytocin alone if the cervix is favourable but that a prostaglandin or a mechanical method (Foley catheter) should be used to ripen an unfavourable cervix before induction. However, UK guidelines[4] consider vaginal dinoprostone (prostaglandin E_2) to have advantages over both amniotomy and oxytocin in terms of comfort, convenience, and acceptability, and recommend it as the preferred method, regardless of cervical status.

As prostaglandins can both ripen the cervix and initiate uterine activity, they induce labour that is similar to spontaneous labour.[1] The intravenous and oral routes have been associated with frequent adverse, particularly gastrointestinal, effects[9,10] and intravaginal dosage is now preferred. The intracervical route is no more effective than the intravaginal route, and is no longer recommended.[4] Dinoprostone is the most widely used prostaglandin and has been given by various routes, but is usually given intravaginally. A systematic review[11] considered the clinical benefits of vaginal gel, vaginal tablets, and pessaries, to be equivalent. The use of a modified-release vaginal insert was also effective, and associated with a reduction in instrumental vaginal delivery compared with gel or tablets, particularly in women with an unfavourable cervix. Dinoprostone was associated with an increased risk of uterine hyperstimulation with fetal heart rate changes.

Whenever possible, amniotomy should be performed in women with intact membranes before giving oxytocin.[6] If vaginal prostaglandins have already been given, usually to ripen the cervix,[2,6] oxytocin should not be started for at least 6 hours. Oxytocin is given by slow intravenous infusion, adjusted according to response.[2,6] Various dosage regimens have been tried, and studies have reported using initial doses ranging from 0.5 to 6 milliunits/minute, dose increases of 1 to 6 milliunits/minute, and intervals between increases of 15 to 40 minutes.[1] Higher doses and shorter intervals between increases can shorten labour and reduce rates of intra-amniotic infection and caesarean delivery, but cause more uterine hyperstimulation.[1,7] Low-dose regimens are now generally advocated.[1,6] There has been some interest in pulsed administration of oxytocin for induction to mimic the pulsatile secretion of endogenous oxytocin that occurs during spontaneous labour, but such use has not been established.[1]

Misoprostol has also been investigated.[1,12,13] Most studies have used the intravaginal route and have suggested it may be more effective than standard methods of labour induction.[14] Oral misoprostol may have a similar efficacy to intravaginal use.[15] However, the risk of uterine hyperstimulation may be increased with misoprostol, more so with the vaginal route than when given orally, and there is as yet insufficient evidence of its safety to recommend routine use.

The antiprogestogen mifepristone also produces cervical dilatation and stimulates uterine contraction and has been tried for cervical ripening and for induction of labour. A systematic review of studies found that it may be effective, but its place in therapy has yet to be established.[16]

In pregnancies at term, *prelabour rupture of the fetal membranes* may be treated with early induction of labour or expectant management (waiting for labour to occur naturally, which will start within 24 hours in most women[17]). There have been concerns that prolonged rupture of membranes may result in higher rates of maternal and neonatal infection, but that induction may result in more caesarean deliveries.[13] A systematic review[17] of studies in women with prelabour rupture of membranes at 37 weeks or later, comparing induction (oxytocin infusion or intravaginal dinoprostone) with expectant management found no difference in rates of caesarean section or instrumental vaginal births. There were lower rates of chorioamnionitis and endometritis in women treated with induction. In neonates, there was no difference in infection rate, but fewer admissions to the intensive care unit after oxytocin use. Women were also more satisfied with induction than expectant management. Intravaginal dinoprostone has been recommended as a less invasive treatment than intravenous oxytocin.[4] Oral and vaginal misoprostol have also been investigated in this group, and may have a similar efficacy to oxytocin and dinoprostone.[13]

A regimen of oral mifepristone, followed by vaginal dinoprostone or vaginal misoprostol, has been recommended for the management of *intra-uterine fetal death* at 24 weeks of gestation or later.[4] Vaginal misoprostol alone may also be effective for labour induction in the management of fetal anomaly or intra-uterine fetal death; it appears to be as effective as other prostaglandins and more effective than oral use.[18]

Labour augmentation may be started when labour is abnormally slow (dystocia) due to atony. Oxytocin is generally used, in similar doses to those for induction.[6] As for induction, both high- and low-dose regimens have been described, with higher doses reducing the duration of labour and rate of caesarean deliveries, but causing more hyperstimulation.[3] Augmentation using oxytocin results in normal vaginal delivery in about half of all women treated.[19]

Intravaginal dinoprostone has also been used for augmentation of labour. A placebo-controlled study[20] in women with slow cervical dilatation found doses of 1 or 2 mg to be effective for improving cervical dilatation and reducing the time to delivery; women given the higher dose were less likely to require oxytocin augmentation after 6 hours, but were at greater risk of hyperstimulation.

Once delivery has successfully been initiated, management of the third stage of labour may be considered to reduce the risks of postpartum haemorrhage (see p. 2130.2).

1. Sanchez-Ramos L. Induction of labor. *Obstet Gynecol Clin North Am* 2005; 32: 181–200.
2. MacKenzie IZ. Induction of labour at the start of the new millennium. *Reproduction* 2006; 131: 989–98.
3. American College of Obstetrics and Gynecology Committee on Practice Bulletins—Obstetrics. Dystocia and augmentation of labor (practice bulletin number 49, December 2003). *Obstet Gynecol* 2003; 102: 1445–54.
4. National Collaborating Centre for Women's and Children's Health/NICE. Induction of labour (issued July 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG070FullGuideline.pdf (accessed 17/09/09)
5. Boulvain M, *et al.* Membrane sweeping for induction of labour. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2005 (accessed 30/06/08).
6. WHO. *Managing complications in pregnancy and childbirth: a guide for midwives and doctors.* Geneva: WHO, 2000. Also available at: http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf (accessed 23/08/10)
7. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. Induction of labor (practice bulletin number 107, August 2009). *Obstet Gynecol* 2009; 114: 386–97.
8. Heinemann J, *et al.* Do mechanical methods of cervical ripening increase infectious morbidity? A systematic review. *Am J Obstet Gynecol* 2008; 199: 177–87.
9. Luckas M, Bricker L. Intravenous prostaglandin for induction of labour. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2000 (accessed 30/06/08).
10. French L. Oral prostaglandin E2 for induction of labour. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2001 (accessed 30/06/08).

The symbol † denotes a preparation no longer actively marketed

11. Kelly AJ, *et al.* Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 12/05/10).
12. Hofmeyr GJ. Induction of labour with an unfavourable cervix. *Best Pract Res Clin Obstet Gynaecol* 2003; 17: 777–94.
13. Crane JMG, Young DC. Induction of labour with a favourable cervix and/or pre-labour rupture of membranes. *Best Pract Res Clin Obstet Gynaecol* 2003; 17: 795–809.
14. Hofmeyr GJ, *et al.* Vaginal misoprostol for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 09/02/11).
15. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
16. Hapangama D, Neilson JP. Mifepristone for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 18/09/09).
17. Dare MR, *et al.* Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 30/06/08).
18. Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 09/02/11).
19. Bugg GJ, *et al.* Outcomes of labours augmented with oxytocin. *Eur J Obstet Gynecol Reprod Biol* 2006; 124: 37–41.
20. Oppenheimer LW, *et al.* Prostaglandin E_2 vaginal gel to treat dystocia in spontaneous labour: a multicentre randomised placebo-controlled trial. *BJOG* 2005; 112: 612–18.

Lactation inhibition and induction

Lactation is the physiological secretion of milk post partum. Milk production by the breast is induced by prolactin while oxytocin promotes milk ejection into the milk ducts; both prolactin and oxytocin secretion are stimulated by suckling.

Lactation inhibition. The breast engorgement with consequent discomfort and galactorrhoea triggered by prolactin secretion post partum can be problematic in women who choose not to breast feed or are unable to do so. Nonsteroidal or synthetic oestrogens were historically used to suppress lactation in such women, but this use is now considered inappropriate because of an increased risk of thromboembolism. Bromocriptine is a potent inhibitor of prolactin secretion: it has been given post partum in short treatment courses (about 14 days) to suppress lactation. However, it has also been associated with severe adverse effects, and its use for lactation suppression is no longer advocated in some countries. Other dopaminergics with similar actions such as cabergoline, lisuride, metergoline, and quinagolide have also been used to suppress lactation. Although it has been suggested that cabergoline, which is generally better tolerated than bromocriptine, may be a better choice for lactation inhibition,[1] the same general objections as for bromocriptine apply to all these drugs. A study in HIV-infected women requiring lactation suppression (in order to prevent mother-to-child transmission from breast milk) found that a combined oral contraceptive was as effective as bromocriptine.[2] Non-pharmacological methods include warm showers to induce milk leakage and reduce pressure, ice packs to reduce local pain and swelling, and a well fitting supportive brassiere. The removal of just enough milk to reduce the pressure but not enough to empty the breasts may help to reduce milk production gradually. Active treatments including mild analgesics such as ibuprofen or paracetamol are also advocated.[3] However, neither pharmacological nor non-pharmacological methods of lactation inhibition have been well evaluated,[4,5] and one review[4] noted that mild analgesia might not be enough to prevent the considerable pain felt by many women.

Lactation induction. Drug therapy has sometimes been used to help stimulate lactation, although good maternal education and support in techniques that promote physiological lactation remain the most important methods.[6] Dopamine antagonists, of which metoclopramide has been the most widely used, can produce modest increases in breast milk production but carry a risk of adverse effects including dystonias. If used, such therapy should be limited to 1 or 2 weeks;[7] there has also been some concern about the presence of these drugs in breast milk.[6,7] The efficacy of metoclopramide in stimulating lactation in women with preterm deliveries has been questioned by a controlled study.[8] Domperidone has also been reported to increase milk production,[7,9] and may cause fewer adverse central effects than metoclopramide. Nevertheless, the FDA has warned against the use of domperidone because of the potential risks of adverse effects in both mother and infant.[10] Protirelin has been given intranasally to stimulate lactation by increasing serum prolactin concentrations,[7] but is expensive, and a suitable commercial preparation is unavailable. Although oxytocin nasal spray has been tried to promote milk ejection, a double-blind, placebo-controlled study[11] of women expressing milk for preterm infants found that although milk production increased marginally in the first 2 days with oxytocin, there was no difference overall after 5 days. Most mothers also believed that they were receiving the active spray suggesting a significant placebo effect. Others[12] warn that its use may interfere with the mother's ability to learn to eject milk naturally, resulting in some becoming dependent upon its action. It might, however, facilitate milk let-down in tetraplegic women.[6]

1. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety* 1996; 14: 228–38. Correction. *ibid.*: 342.
2. Piya-Anant M, *et al.* The combined oral contraceptive pill versus bromocriptine to suppress lactation in puerperium: a randomized double blind study. *J Med Assoc Thai* 2004; 87: 670–3.
3. Moore DB, Catlin A. Lactation suppression: forgotten aspect of care for the mother of a dying child. *Pediatr Nurs* 2003; 29: 383–4.
4. Spitz AM, *et al.* Treatment for lactation suppression: little progress in one hundred years. *Am J Obstet Gynecol* 1998; 179: 1485–90.
5. Oladapo OT, Fawole B. Treatments for suppression of lactation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 26/01/11).
6. Anderson PO, Valdés V. A critical review of pharmaceutical galactagogues. *Breastfeed Med* 2007; 2: 229–42.
7. Gabay MP. Galactogogues: medications that induce lactation. *J Hum Lact* 2002; 18: 274–9.
8. Hansen WF, *et al.* Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstet Gynecol* 2005; 105: 383–9.
9. da Silva OP, *et al.* Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial. *Can Med Assoc J* 2001; 164: 17–21.
10. FDA. FDA warns against women using unapproved drug, domperidone, to increase milk production (issued 7th June, 2004). Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm (accessed 22/08/10)
11. Fewtrell MS, *et al.* Randomised, double blind trial of oxytocin nasal spray in mothers expressing breast milk for preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006; 91: F169–F174.
12. Anderson PO, Valdés V. Increasing breast milk supply. *Clin Pharm* 1993; 12: 479–80.

Postpartum haemorrhage

If the uterus fails to contract adequately after delivery (uterine atony), or if retained placental remnants prevent retraction of the placental bed, postpartum haemorrhage may occur. These two causes account for about 80% of cases of postpartum haemorrhage; in the remainder it is usually due to trauma of the genital tract or coagulopathy.

Primary postpartum haemorrhage has traditionally been defined as vaginal bleeding of more than 500 mL within 24 hours after childbirth. However, the volume of blood loss is often underestimated and the ability of a woman to cope with blood loss may be affected by her previous health, anaemia, and hypovolaemia.[1-3] Postpartum haemorrhage may be fatal to the mother unless promptly dealt with, and **management** generally involves:

- removal of the placenta if it has not been expelled
- the use of oxytocics to contract the uterus
- transfusion if blood loss is severe

Parenteral oxytocin is the oxytocic generally used to control bleeding due to uterine atony,[3,4] and oxytocin infusion may be used to maintain uterine contraction.[2] An ergot alkaloid (ergometrine or methylergometrine),[1,3] or the fixed combination *Syntometrine* (oxytocin and ergometrine),[4] may be used as an alternative or for bleeding that does not respond to oxytocin. Prostaglandins such as carboprost or dinoprostone may also be used,[1,3] usually for haemorrhage that has not been controlled by oxytocin and ergot preparations.[2,4] There is considerable interest in the use of misoprostol, particularly for developing countries,[5,6] because of its better stability and ease of administration.[2] It has been used both rectally and sublingually, but a review[7] found there was insufficient evidence to support the use of rectal misoprostol instead of a combination of oxytocin and ergometrine, and studies of sublingual misoprostol have confirmed that oxytocin is preferred.[8,9] Nevertheless, in women who have not been given prophylactic oxytocics during labour misoprostol could be used for treatment when oxytocin is not available, although the optimum dose remains to be determined.[9] Surgery may be required if medical management does not control bleeding.[1,2]

Oxytocin may be used in the management of retained placenta, given by intramuscular injection[3] or injected into the vein of the umbilical cord[4] (although there is growing evidence that umbilical use may be of no benefit—see p. 2144.1). However, ergometrine is not recommended because it causes tetanic uterine contractions, which may delay expulsion of the placenta.[3,4] Dinoprostone and sulprostone are also not recommended, because of a lack of evidence of efficacy, and concerns about adverse cardiovascular effects.[4]

Secondary postpartum haemorrhage occurs between 24 hours and 12 weeks after delivery and although associated with maternal morbidity rather than death in developed countries, it is a major contributor to maternal death in developing countries. Antibacterials, oxytocics, hormone therapy, and a variety of surgical treatments are used,[1,3,10] but a systematic review[10] concluded that evidence for the best treatment is lacking.

Risk factors for postpartum haemorrhage include prolonged labour, augmented labour, overdistended uterus (for example in multiple pregnancy), and a history of postpartum haemorrhage.[1] However, atonic postpartum haemorrhage occurs in many women without identifiable risk factors, and authorities recommend that **prophylaxis** should be offered to all women during childbirth.[11,12] *Active management of the third stage of labour* involves prophylactic use of an oxytocic, cord clamping before placental delivery, controlled cord traction, and uterine massage after delivery of the placenta.

The routine use of active management, with oxytocics usually given after delivery of the anterior shoulder or immediately after delivery of the baby, reduces blood loss and the risk of postpartum haemorrhage, although this may not be significant for women at low risk of bleeding.[13] However, despite the widespread use of oxytocics there is limited evidence of high quality comparing different drugs. Oxytocin[14] and ergot alkaloids[15] (usually ergometrine) can both reduce postpartum blood loss and appear to be equally effective,[14] while *Syntometrine* may be more effective than oxytocin alone in reducing the risk of moderate postpartum haemorrhage (500 to 1000 mL).[16] However, ergot alkaloids and *Syntometrine* cause more adverse effects than oxytocin, particularly nausea, vomiting, and raised blood pressure.[14,16] Although the quality of evidence is low, WHO recommends that oxytocin is generally preferred for prevention of postpartum haemorrhage; an ergot alkaloid (ergometrine or methylergometrine) or *Syntometrine* may be used if oxytocin is not available.[12]

Prostaglandins, and in particular misoprostol, have also been investigated as an alternative for the routine management of the third stage of labour. Although oral or sublingual misoprostol may reduce the risk of severe postpartum haemorrhage (more than 1000 mL), it is less effective than conventional injectable oxytocics.[17] Data on other prostaglandins are scarce.[17] Based on these findings, a systematic review[17] has suggested that prostaglandins are not preferrable to oxytocin, but that misoprostol may be used where no injectable oxytocic is available. Others have also argued that although misoprostol may be less effective, it would still be useful in developing countries where there are no alternatives,[8,18] and some authorities include misoprostol as an option when other oxytocics are not available or the birth attendant's skills are limited.[6,11,12]

Where a skilled attendant is not available to provide active management, an appropriately trained healthcare worker may give oxytocin or misoprostol alone for the prevention of postpartum haemorrhage.[12]

1. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. Postpartum hemorrhage (ACOG Practice Bulletin, number 76, issued October 2006). *Obstet Gynecol* 2006; 108: 1039–47.
2. Ramanathan G, Arulkumaran S. Postpartum hemorrhage. *J Obstet Gynaecol Can* 2006; 28: 967–73.
3. WHO. *Managing complications in pregnancy and childbirth: a guide for midwives and doctors.* Geneva: WHO, 2000. Also available at: http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf (accessed 23/08/10)
4. WHO. WHO guidelines for the management of postpartum haemorrhage and retained placenta (issued 2009). Available at: http://whqlibdoc.who.int/publications/2009/9789241598514_eng.pdf (accessed 17/09/09)
5. Hofmeyr GJ, *et al.* Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG* 2005; 112: 547–53.
6. International Confederation of Midwives, International Federation of Gynaecologists and Obstetricians. Prevention and treatment of postpartum haemorrhage: new advances for low resource settings (issued 2006). Available at: *http://www.pphprevention.org/files/FIGO-ICM_Statement_November2006_Final.pdf* (accessed 30/06/08) or http://www.figo.org/files/figo-corp/docs/PPH%20Joint%20Statement%202%20English.pdf (accessed 22/08/10)
7. Mousa HA, Alfirevic Z. Treatment for primary postpartum haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 30/06/08).
8. Anonymous. Misoprostol for postpartum haemorrhage. *Drug Ther Bull* 2010; 48: 66–9.
9. Buekens P, Althabe F. Post-partum haemorrhage: beyond the confrontation between misoprostol and oxytocin. *Lancet* 2010; 375: 176–8.
10. Alexander J, *et al.* Treatments for secondary postpartum haemorrhage. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2002 (accessed 30/06/08).
11. International Confederation of Midwives, International Federation of Gynaecologists and Obstetricians. Management of the third stage of labour to prevent post-partum haemorrhage (issued 2003). Available at: http://www.figo.org/files/figo-corp/docs/PPH%20Joint%20Statement.pdf (accessed 22/08/10)
12. WHO. WHO recommendations for the prevention of postpartum haemorrhage (issued 2007). Available at: http://apps.who.int/rhl/effective_practice_and_organizing_care/guideline_2007_WHO_Recommendations_for_prevention_of_PPH.pdf (accessed 22/08/10)
13. Begley CM, *et al.* Active versus expectant management for women in the third stage of labour. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2010 (accessed 04/02/11).
14. Cotter AM, *et al.* Prophylactic oxytocin for the third stage of labour Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2001 (accessed 30/06/08).
15. Liabsuetrakul T, *et al.* Prophylactic use of ergot alkaloids in the third stage of labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 30/06/08).
16. McDonald SJ, *et al.* Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 30/06/08).
17. Gülmezoglu AM, *et al.* Prostaglandins for preventing postpartum haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).
18. Langenbach C. Misoprostol in preventing postpartum hemorrhage: a meta-analysis. *Int J Gynecol Obstet* 2006; 92: 10–18.

Premature labour

Premature labour (preterm labour) is the onset of labour before the expected date, resulting in delivery of an immature infant. Conventionally the definition includes women giving birth before 37 weeks of gestation but in practice most problems arise with births before 32 to 34 weeks.[1-3] Risk factors for premature labour include infection, premature rupture of the membranes, cervical incompetence, and multiple pregnancy. There are few proven measures to *prevent premature labour*, but cervical cerclage (temporary surgical closure of the cervix) may be used for cervical incompetence,[4] and treatment of infections is being investigated.[5] In women with premature rupture of the membranes who have not gone into spontaneous labour there is some evidence that antibacterial therapy may be effective in delaying delivery and improving outcomes (see Premature Labour, p. 201.3). The value of prophylactic tocolysis, using drugs to prevent the onset of uterine contractions, is unclear[6,7] and such therapy is not recommended.[8] In women who have a history of spontaneous premature delivery, there is some evidence to suggest that a prophylactic progestogen such as hydroxyprogesterone caproate may reduce the risk for premature delivery in subsequent pregnancies.[9,10]

A diagnosis of premature labour is not always easy to make and evidence of cervical change should usually be present in addition to uterine activity.[2,3,11] Once a diagnosis has been established, a decision must be made as to whether to postpone delivery by *acute tocolysis*, using drugs that inhibit uterine contractions. It may not be considered appropriate to stop labour in some women. However, in patients of about 24 to 34 weeks of gestation without complications, attempts to postpone delivery are usually worth trying, if only in the short-term, to allow emergency treatment such as corticosteroids to be given to the mother to enhance the maturation of the fetal respiratory system (see Neonatal Respiratory Distress Syndrome, p. 1608.3) and to enable the patient to be transferred to a specialised unit for preterm delivery.[1-3,11] In the presence of ruptured membranes, tocolysis is rarely considered necessary after this time (some recommend 32 weeks of gestation[2] while others recommend 36 weeks[3]).

- The commonest tocolytics have historically been the beta-adrenoceptor agonists, which relax the smooth muscle of the uterus by stimulation of $beta_2$-adrenoceptors.[12] Nonselective agonists, for example orciprenaline and isoxsuprine, have been replaced by more selective $beta_2$ agonists such as ritodrine, salbutamol, and terbutaline. These can postpone labour for a few days[13,14] and the preferred route for starting treatment is subcutaneous or intravenous infusion.[12] Oral or subcutaneous maintenance therapy with $beta_2$ agonists after successful treatment of an episode of acute premature labour produces no further benefit[15,16] (see also Maintenance Therapy, below). There is little evidence that $beta_2$ agonists significantly reduce perinatal mortality rates.[17] The patient may have adverse cardiovascular and metabolic effects and, in particular, pulmonary oedema has been reported in some women given $beta_2$ agonists intravenously to suppress labour (see p. 1222.3). It is therefore essential that the patient's heart rate and state of hydration are carefully monitored throughout infusion. In the event of caesarean section beta blockers may be needed to combat an increased tendency to uterine bleeding.
- More recently, calcium-channel blockers have been shown to be effective tocolytics, presumably by their action on myometrial calcium.[12] Most experience concerns nifedipine, which has been reported to be at least as effective as, and possibly better than, $beta_2$ agonists or magnesium in delaying labour,[18-20] although a systematic review[21] considered the quality of many of the studies reporting efficacy to be poor. It has the advantage that it can be given orally,[12] and some favour its use as a first-line drug,[1,19] although it is not licensed in the UK for this use. Nicardipine has also produced favourable results.[22] Others have expressed concern about the safety of calcium-channel blockers,[23] and some suggest that they should be used with caution.[2,3] Maintenance nifedipine therapy appears to be of no benefit after preterm labour has been controlled.[24]
- Atosiban is a peptide analogue of oxytocin with oxytocin antagonist properties. A pooled analysis[25] of three controlled studies, and a systematic review,[26] found atosiban to be as effective as beta agonists in the management of premature labour, with fewer maternal cardiovascular adverse effects. These findings were supported by a large open-label study[27] of women treated with atosiban or usual care (usually a beta agonist). A large cohort study also found a lower risk of adverse effects associated with atosiban compared with beta agonists and nifedipine.[28] Some clinicians favour atosiban as a first-line tocolytic in preference to the traditional drugs.[1-3]
- Parenteral magnesium sulfate is thought to act as a tocolytic by calcium antagonism at the neuromuscular junction.[12] Although it has been generally considered to be as effective as the $beta_2$ agonists,[12] a systematic review[29] concluded that it was ineffective at delaying birth or preventing preterm birth, and it has been suggested that tocolytic use of magnesium may be associated with increased paediatric mortality—see p. 1789.1. To decrease the risk of overdose, magnesium sulfate should only be given from a controlled pump.[12] Oral magnesium has been tried but has not been shown to be effective.[12] Although magnesium sulfate is the most widely used tocolytic in the USA, the American College of Obstetricians and Gynecologists does not promote it (or any drug) for first-line tocolysis.[11] It is not recommended in Europe,[3] and some in the USA have called for such use to be stopped.[30,31]
- Prostaglandins have a role in the induction of labour as mediators of uterine contractions and cervical softening and dilatation. Cyclo-oxygenase (prostaglandin synthetase) inhibitors, particularly indometacin, have therefore been given orally or rectally to inhibit premature labour.[12,32] Although this treatment may be as effective as ritodrine,[33,34] adverse effects on the fetus have been reported, such as oligohydramnios, intraventricular haemorrhage, necrotising enterocolitis, and oliguria.[32] The most widely reported complication has been constriction of the fetal ductus arteriosus; pulmonary vascular hypertrophy can develop after prolonged constriction. Sensitivity of the ductus arteriosus appears to increase with gestational age, and indometacin therapy should therefore be limited to gestations of less than 32 weeks. If therapy is to continue for longer than 72 hours, the ductus arteriosus should be monitored for evidence of constriction. An increased incidence of persistent patent ductus arteriosus in the newborn has also been reported after indometacin tocolysis, although an association has been questioned.[32] A systematic review[35] of observational and randomised studies found no significant increase overall in the risk of neonatal complications in infants who had been exposed to indometacin tocolysis compared with infants who had not. However, the data had limited statistical power and the review was unable to exclude the possibility that indometacin may increase the risk of adverse neonatal outcomes. The evidence for efficacy of cyclo-oxygenase inhibitors is based on small studies,[36] and because of the potential for adverse effects, indometacin is generally reserved as a second-line drug or given with other tocolytics for an additive effect.[12] More recently it has been suggested that the enzyme isoform cyclo-oxygenase-2 is associated with labour, while cyclo-oxygenase-1 is responsible for constant prostaglandin synthesis in body tissues. The role of cyclo-oxygenase-2 inhibitors in the treatment or prevention of premature labour remains investigational.
- Other drugs are under investigation. Application of patches of the nitric oxide donor glyceryl trinitrate to the abdomen to produce uterine relaxation was reported to be as effective as ritodrine treatment.[37] However, another study[38] found transdermal glyceryl trinitrate to be less effective than beta agonists, and a systematic review[39] concluded that there was insufficient evidence to support its routine use.

When acute tocolysis has successfully suppressed uterine activity, the use of *maintenance therapy* has been tried to prevent recurrent episodes of premature labour. However, a systematic review[40] found that although there was a small but significant increase in the number of days gained before delivery, maintenance therapy with tocolytics such as selective $beta_2$ agonists, calcium-channel blockers, atosiban, and cyclo-oxygenase inhibitors did not reduce the incidence of premature birth or recurrent premature labour; there was also a non-significant trend towards an increase in adverse perinatal outcomes. Maintenance therapy is not recommended for routine use.[1,3,11]

1. Royal College of Obstetricians and Gynaecologists. Tocolytic drugs for women in preterm labour (issued October 2002). Available at: http://www.rcog.org.uk/files/rcog-corp/GT1RTocolyticDrug2002revised.pdf (accessed 22/08/10)
2. Lamont RF, International Preterm Labour Council. Evidence-based labour ward guidelines for the diagnosis, management and treatment of spontaneous preterm labour. *J Obstet Gynaecol* 2003; 23: 469–78.
3. 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)
4. Romero R, *et al.* The role of cervical cerclage in obstetric practice: can the patient who could benefit from this procedure be identified? *Am J Obstet Gynecol* 2006; 194: 1–9.
5. Morency A-M, Bujold E. The effect of second-trimester antibiotic therapy on the rate of preterm birth. *J Obstet Gynaecol Can* 2007; 29: 35–44.
6. Mercer BM. Is there a role for tocolytic therapy during conservative management of preterm premature rupture of the membranes? *Clin Obstet Gynecol* 2007; 50: 487–96.
7. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics. Premature rupture of membranes (ACOG Practice Bulletin number 80, issued April 2007). *Obstet Gynecol* 2007; 109: 1007–19.
8. Royal College of Obstetricians and Gynaecologists. Preterm prelabour rupture of membranes (issued November 2006). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT44PretermPrelabourRupture2006.pdf (accessed 22/08/10)
9. Sanchez-Ramos L, *et al.* Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. *Obstet Gynecol* 2005; 105: 273–9.
10. Dodd JM, *et al.* Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 17/09/09).
11. American College of Obstetricians and Gynaecologists Committee on Practice Bulletins. Management of preterm labor (ACOG Practice Bulletin number 43, issued May 2003). *Obstet Gynecol* 2003; 101: 1039–47.
12. Katz VL, Farmer RM. Controversies in tocolytic therapy. *Clin Obstet Gynecol* 1999; 42: 802–19.
13. Anouyanouth S, *et al.* Betamimetics for inhibiting preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 30/06/08).
14. Lam F, Gill P. β-Agonist tocolytic therapy. *Obstet Gynecol Clin North Am* 2005; 32: 457–84.
15. Sanchez-Ramos L, *et al.* Efficacy of maintenance therapy after acute tocolysis: a meta-analysis. *Am J Obstet Gynecol* 1999; 181: 484–90.
16. Dodd JM, *et al.* Oral betamimetics for maintenance therapy after threatened preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 30/06/08).
17. The Canadian Preterm Labor Investigators Group. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. *N Engl J Med* 1992; 327: 308–12.
18. Ray JG. Meta-analysis of nifedipine versus beta-sympathomimetic agents for tocolysis during preterm labour. *J Soc Obstet Gynaecol Can* 1998; 20: 259–69.
19. Tsatsaris V, *et al.* Tocolysis with nifedipine or beta-adrenergic agonists: a meta-analysis. *Obstet Gynecol* 2001; 97: 840–7.
20. King JF, *et al.* Calcium channel blockers for inhibiting preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 30/06/08).
21. Lamont RF, *et al.* Steering Group of the International Preterm Labour Council. The quality of nifedipine studies used to assess tocolytic efficacy: a systematic review. *J Perinat Med* 2005; 33: 287–95.
22. Jannet D, *et al.* Nicardipine versus salbutamol in the treatment of premature labor: a prospective randomized study. *Eur J Obstet Gynecol Reprod Biol* 1997; 73: 11–16.
23. Oei SG. Calcium channel blockers for tocolysis: a review of their role and safety following reports of serious adverse events. *Eur J Obstet Gynecol Reprod Biol* 2006; 126: 137–45.
24. Lyell DJ, *et al.* Maintenance nifedipine tocolysis compared with placebo: a randomized controlled trial. *Obstet Gynecol* 2008; 112: 1221–6.
25. The Worldwide Atosiban versus Beta-agonists Study Group. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. *Br J Obstet Gynaecol* 2001; 108: 133–42.
26. Papatsonis D, *et al.* Oxytocin receptor antagonists for inhibiting preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 30/06/08).
27. Husslein P, *et al.* Atosiban versus usual care for the management of preterm labor. *J Perinat Med* 2007; 35: 305–13.
28. de Heus R, *et al.* Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. Abridged version: *BMJ* 2009; 338: 758–60. Full version: http://www.bmj.com/content/338/bmj.b744.full.pdf (accessed 07/02/11)
29. 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 30/06/08).
30. Grimes DA, Nanda K. Magnesium sulfate tocolysis: time to quit. *Obstet Gynecol* 2006; 108: 986–9.
31. Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med* 2007; 357: 477–87.
32. Vermillion ST, Landen CN. Prostaglandin inhibitors as tocolytic agents. *Semin Perinatol* 2001; 25: 256–62.
33. Morales WJ, *et al.* Efficacy and safety of indomethacin versus ritodrine in the management of preterm labor: a randomized study. *Obstet Gynecol* 1989; 74: 567–72.
34. Besinger RE, *et al.* Randomized comparative trial of indomethacin and ritodrine for the long-term treatment of preterm labor. *Am J Obstet Gynecol* 1991; 164: 981–8.
35. Loe SM, *et al.* Assessing the neonatal safety of indomethacin tocolysis: a systematic review with meta-analysis. *Obstet Gynecol* 2005; 106: 173–9.
36. King JF, *et al.* Cyclo-oxygenase (COX) inhibitors for treating preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 30/06/08).
37. Lees CC, *et al.* Glyceryl trinitrate and ritodrine in tocolysis: an international multicenter randomized study. *Obstet Gynecol* 1999; 94: 403–8.
38. Bisits A, *et al.* The Randomized Nitric Oxide Tocolysis Trial (RNOTT) for the treatment of preterm labor. *Am J Obstet Gynecol* 2004; 191: 683–90.
39. Duckitt K, Thornton S. Nitric oxide donors for the treatment of preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 30/06/08).
40. Sanchez-Ramos L, Huddleston JF. The therapeutic value of maintenance tocolysis: an overview of the evidence. *Clin Perinatol* 2003; 30: 841–54.

Termination of pregnancy

Termination of pregnancy can be achieved medically or surgically. Uterine aspiration is a common method used for *surgical termination*; before 13 weeks of pregnancy it is usually termed suction or vacuum curettage, and after 13 weeks as dilatation and evacuation.[1] Cervical dilatation becomes increasingly necessary as gestation progresses and has been recommended for all pregnancies of more than 10 weeks, for pregnancies over 9 weeks in nulliparous women, and for all women younger than 18 years of age.[2,3] It may be achieved by using mechanical dilators, laminaria or synthetic hygroscopic dilators,[1,3] mifepristone, or a prostaglandin such as gemeprost or misoprostol.[1-3] Various drugs, used alone and in combination, have been tried for *medical termination* of pregnancy. Prostaglandins ripen the cervix and stimulate uterine contractility. They can bring

about successful termination when used alone, but the high doses required can cause significant adverse effects.[4-6] The most commonly used prostaglandins are gemeprost and misoprostol;[3,4] others that have been used include carboprost and sulprostone, but these have been associated with more severe adverse effects.[3] The antiprogestogen mifepristone also ripens the cervix and stimulates uterine contractility; in addition, it increases the sensitivity of the myometrium to prostaglandins with a maximum effect about 24 to 48 hours after dosing. Mifepristone is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with a prostaglandin, usually gemeprost or misoprostol, to achieve expulsion of the uterine contents.[3-5,7,8] The antimetabolite methotrexate has also been used with misoprostol, but it has a delayed effect and the time from induction to abortion can be several days or weeks.[4,5] Other methods that have been used for termination of pregnancy, particularly in the second trimester, include intra-amniotic use of dinoprost, hypertonic sodium chloride, or hyperosmolar urea augmented with oxytocin, carboprost, or dinoprost.[1]

Uterine cramping and bleeding are associated with both surgical and medical termination processes. Surgical termination may be carried out under conscious sedation,[1,2] local anaesthesia using paracervical block,[1-3] or general anaesthesia.[2] Analgesia requirements in medical termination may be higher in younger women, nulliparous women, and those with longer gestations.[3,4] Analgesics such as paracetamol, NSAIDs, and codeine are commonly used.[6] Generally, bleeding lasts longer after medical termination than after vacuum aspiration.[6] With medical termination using mifepristone plus a prostaglandin, bleeding is initially heavy but gradually diminishes over about 2 weeks, although minor bleeding can continue for longer.[1,6]

Factors influencing the choice of method for termination include the stage of gestation, availability of surgical services and abortifacient drugs, and the woman's preference. The most common approaches are outlined below.

- In the early first trimester (up to 49 days) a medical method, using mifepristone followed by a prostaglandin, is preferred because the failure rate is higher with vacuum aspiration.[2,6] Methotrexate followed by a prostaglandin is an alternative at this early stage,[1,5] but expulsion can take several days or weeks.[4] Either a surgical or medical method can be used between 49 and 63 days of gestation. However, oral misoprostol for medical termination becomes less effective as gestation progresses[4,5] so a vaginal prostaglandin is preferred.[2,5,6]
- In the late first trimester (up to 13 weeks) a surgical or medical method may be used. After 9 or 10 weeks of gestation, cervical preparation is used before surgical procedures and multiple doses of prostaglandin may be needed to achieve medical termination.[2]
- In mid-trimester termination (13 to 24 weeks) a surgical or medical method may be used. Cervical preparation is essential before surgical termination and multiple doses of prostaglandin will generally be required for medical termination.[2,3]

Some of the methods used for termination of pregnancy are also used to hasten miscarriage after **early pregnancy loss** (less than 12 weeks of gestation). Surgical evacuation is effective but associated with a higher risk of infection than expectant management.[9,10] Vaginal misoprostol can also hasten miscarriage, but oral use is less effective.[11] The success of medical treatment may also depend on the type of loss;[10] incomplete miscarriage may be managed with a prostaglandin alone, while missed miscarriage may require a higher dose and longer duration of prostaglandin treatment, or the addition of mifepristone.[12] Miscarriage or early fetal death occurring in the second trimester may be managed similarly. For the management of intra-uterine fetal death in later pregnancy, see Labour Induction and Augmentation, p. 2129.1.

1. Stubblefield PG, *et al.* Methods for induced abortion. *Obstet Gynecol* 2004; **104**: 174–85.
2. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7 (issued September 2004). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/NEBInducedAbortionfull.pdf (accessed 22/08/10)
3. Lalitkumar S, *et al.* Mid-trimester induced abortion: a review. *Hum Reprod Update* 2007; **13**: 37–52.
4. Hamoda H, Flett GMM. Medical termination of pregnancy in the early first trimester. *J Fam Plann Reprod Health Care* 2005; **31**: 10–14.
5. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Medical management of abortion (ACOG practice bulletin number 67, issued October 2005). *Obstet Gynecol* 2005; **106**: 871–82.
6. WHO. Frequently asked clinical questions about medical abortion (2006). Available at: http://whqlibdoc.who.int/publications/2006/9241594845_eng.pdf (accessed 22/08/10)
7. Kulier R, *et al.* Medical methods for first trimester abortion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 30/06/08).
8. Wildschut H, *et al.* Medical methods for mid-trimester termination of pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2011 (accessed 22/03/11).
9. Nanda K, *et al.* Expectant care versus surgical treatment for miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
10. Anonymous. Which approach for first trimester miscarriage? *Drug Ther Bull* 2009; **47**: 77–80.
11. Neilson JP, *et al.* Medical treatment for early fetal death (less than 24 weeks). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 30/06/08).
12. Royal College of Obstetricians and Gynaecologists. The management of early pregnancy loss (issued October 2006, valid until October 2009). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT25ManagementofEarlyPregnancyLoss2006.pdf (accessed 03/02/11)

Aglepristone *(rINN)*

Aglepriston; Aglepristona; Aglépristone; Aglepristoni; Aglepristonum; RU-46534; Аглепристон.

11β-[*p*-(Dimethylamino)phenyl]-17β-hydroxy-17-[(*Z*)-propenyl]estra-4,9-dien-3-one.

$C_{29}H_{37}NO_2$=431.6

CAS — 124478-60-0.

ATC Vet — QG03XB90.

UNII — 0UT4JLE1CM.

Profile

Aglepristone has antiprogestogenic activity and is used in veterinary medicine as an abortifacient in *dogs*.

Atosiban *(BAN, USAN, rINN)*

Atosibaani; Atosibanum; Atozyban; ORF-22164; RWJ-22164; Атозибан.

1-(3-Mercaptopropionic acid)-2-[3-(*p*-ethoxyphenyl)-D-alanine]-4-L-threonine-8-L-ornithineoxytocin; [1-(3-Sulfanylpropanoyl),2-(4-*O*-ethyltyrosine),4-L-threonine-8-L-ornithine] oxytocin.

$C_{43}H_{67}N_{11}O_{12}S_2$=994.2

CAS — 90779-69-4.

ATC — G02CX01.

ATC Vet — QG02CX01.

UNII — 081D12SI0Z.

Uses and Administration

Atosiban is a peptide analogue of oxytocin (p. 2143.1) but with oxytocin antagonist properties. It is used as a tocolytic in the management of premature labour (p. 2131.1). Atosiban is given intravenously as the acetate, but doses are expressed in terms of the base. An initial bolus dose equivalent to atosiban 6.75 mg is given by intravenous injection (as a solution containing 7.5 mg/mL) over one minute. This is immediately followed by a continuous infusion of 300 micrograms/minute for 3 hours, then 100 micrograms/minute for up to 45 hours, as a solution containing 750 micrograms/mL. The total duration of treatment should not exceed 48 hours, and the total dose should not exceed 330 mg.

Premature labour. References.

1. Romero R, *et al.* An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000; **182**: 1173–83.
2. Valenzuela GJ, *et al.* Maintenance treatment of preterm labor with the oxytocin antagonist atosiban: the Atosiban PTL-098 Study Group. *Am J Obstet Gynecol* 2000; **182**: 1184–90.
3. Moutquin JM, *et al.* Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. *Am J Obstet Gynecol* 2000; **182**: 1191–9.
4. The Worldwide Atosiban versus Beta-agonists Study Group. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. *Br J Obstet Gynaecol* 2001; **108**: 133–42.
5. The European Atosiban Study Group. The oxytocin antagonist atosiban versus the beta-agonist terbutaline in the treatment of preterm labor: a randomized, double-blind, controlled study. *Acta Obstet Gynecol Scand* 2001; **80**: 413–22.
6. French/Australian Atosiban Investigators Group. Treatment of preterm labor with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. *Eur J Obstet Gynecol Reprod Biol* 2001; **98**: 177–85.
7. Coomarasamy A, *et al.* Oxytocin antagonists for tocolysis in preterm labour—a systematic review. *Med Sci Monit* 2002; **8**: RA268–73.
8. Tsatsaris V, *et al.* Atosiban for preterm labour. *Drugs* 2004; **64**: 375–82.
9. Husslein P, *et al.* Atosiban versus usual care for the management of preterm labor. *J Perinat Med* 2007; **35**: 305–13.
10. Sanu O, Lamont RF. Critical appraisal and clinical utility of atosiban in the management of preterm labor. *Ther Clin Risk Manag* 2010; **6**: 191–9.

Adverse Effects and Precautions

Adverse effects reported in women receiving atosiban for premature labour include nausea and vomiting, headache, dizziness, flushes, tachycardia, hypotension, hyperglycaemia, and injection site reactions. Atosiban should not be used where continuation of pregnancy is hazardous to mother or fetus, including where there is uterine haemorrhage requiring immediate delivery, eclampsia or severe pre-eclampsia, intra-uterine growth retardation and abnormal fetal heart rate, suspected intra-uterine infection, placenta praevia, or abruptio placentae. Monitoring of uterine contractions and fetal heart rate is recommended during use, and blood loss should be monitored after delivery.

Although there has been some concern about fetal exposure, licensed product information states that no specific adverse effects on the newborn have been reported.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atosiban 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 30/07/11)

Pharmacokinetics

In women in premature labour, atosiban reaches steady-state plasma concentrations within one hour of the start of infusion, and has a terminal half-life of 1.7 hours after stopping infusion. Atosiban is 46 to 48% bound to plasma proteins, and crosses the placenta. It is metabolised to an active metabolite, which is excreted in the urine; both atosiban and this metabolite are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tractocile; *Austria*: Tractocile; *Belg.*: Tractocile; *Chile*: Tractocile†; *China*: Tractocile (依保); *Cz.*: Tractocile; *Denm.*: Tractocile; *Fin.*: Tractocile; *Fr.*: Tractocile; *Ger.*: Tractocile; *Gr.*: Tractocile; *Hong Kong*: Tractocile; *Hung.*: Tractocile; *Irl.*: Tractocile; *Ital.*: Tractocile; *Malaysia*: Tractocile; *Mex.*: Tractocile; *Neth.*: Tractocile; *Norw.*: Tractocile; *NZ*: Tractocile; *Pol.*: Tractocile; *Port.*: Tractocile; *S.Afr.*: Tractocile; *Spain*: Tractocile; *Swed.*: Tractocile; *Switz.*: Tractocile; *Thai.*: Tractocile; *Turk.*: Tractocile; *UK*: Tractocile; *Ukr.*: Tractocile (Трактоцил).

Carbetocin *(BAN, rINN)*

Carbetocina; Carbétocine; Carbetocinum; Karbetocin; Karbetosiini; Карбетоцин.

2,1-Desamino-4,1-desthio-$O^{4,2}$-methyl[1-homocysteine]oxytocin; 1-Butyric acid-2-[3-(*p*-methoxyphenyl)-L-alanine]oxytocin.

$C_{45}H_{69}N_{11}O_{12}S$=988.2

CAS — 37025-55-1.

ATC — H01BB03.

ATC Vet — QH01BB03.

UNII — 88TWF8015Y.

Uses and Administration

Carbetocin is a synthetic analogue of oxytocin (p. 2143.1) reported to have a longer duration of action. For the prevention of uterine atony and excessive bleeding after caesarean section under epidural or spinal anaesthesia, a single dose of 100 micrograms may be given by slow intravenous injection over 1 minute. Carbetocin must only be given after delivery of the infant, preferably before removal of the placenta.

References.

1. Dansereau J, *et al.* Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. *Am J Obstet Gynecol* 1999; **180**: 670–6.
2. Boucher M, *et al.* Comparison of carbetocin and oxytocin for the prevention of postpartum hemorrhage following vaginal delivery: a double-blind randomized trial. *J Obstet Gynaecol Can* 2004; **26**: 481–8.
3. Leung SW, *et al.* A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. *BJOG* 2006; **113**: 1459–64.
4. Peters NC, Duvekot JJ. Carbetocin for the prevention of postpartum hemorrhage: a systematic review. *Obstet Gynecol Surv* 2009; **64**: 129–35.
5. Rath W. Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. *Eur J Obstet Gynecol Reprod Biol* 2009; **147**: 15–20.

Adverse Effects and Precautions

Carbetocin has similar adverse effects and precautions to those associated with oxytocin when it is used after caesarean section (see p. 2144.1 and p. 2144.2, respectively). However, carbetocin should not be used at any stage of labour before delivery of the infant because its effects on the uterus last for several hours.

Breast feeding. In 5 women who were 7 to 14 weeks postpartum, carbetocin was measured in the breast milk within 90 minutes of a single 70-microgram intramuscular dose.[1] The ratio of milk to plasma concentrations was low, suggesting that very little carbetocin was distributed into breast milk. Licensed UK product information states that no significant effects on milk ejection were reported during clinical studies, and that any carbetocin ingested by a breast-fed infant would probably be degraded by enzymes in the gastrointestinal tract. The last available guidance from the American Academy of Pediatrics considered the

use of carbetocin to be usually compatible with breast feeding.[2]

1. Silcox J, *et al.* Transfer of carbetocin into human breast milk. *Obstet Gynecol* 1993; **82**: 456–9.
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 30/06/08)

Interactions

Although reports are lacking, carbetocin may be involved in similar interactions to those that can occur with oxytocin (p. 2144.3).

Pharmacokinetics

After intravenous injection of carbetocin, firm uterine contraction occurs within 2 minutes and lasts for several hours. Carbetocin undergoes a biphasic elimination, with a terminal elimination half-life of about 40 minutes. Less than 1% of a dose is excreted unchanged by the kidney. Carbetocin is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Duratocin; ***Austral.***: Duratocin; ***Austria***: Pabal; ***Belg.***: Pabal; ***Canad.***: Duratocin; ***Chile***: Duratocin; ***China***: Duratocin (巧特欣); ***Cz.***: Duratocin; ***Denm.***: Pabal; ***Fin.***: Pabal; ***Fr.***: Pabal; ***Ger.***: Pabal; ***Gr.***: Pabal; ***Hong Kong***: Duratocin; ***Hung.***: Pabal; ***Irl.***: Pabal; ***Ital.***: Duratocin; ***Malaysia***: Duratocin; ***Mex.***: Lonactene; ***Neth.***: Pabal; ***Norw.***: Pabal; ***NZ***: Duratocin; ***Philipp.***: Duratocin; ***Pol.***: Pabal; ***Port.***: Pabal; ***Singapore***: Duratocin; ***Spain***: Duratobal; ***Swed.***: Pabal; ***Switz.***: Pabal; ***Thai.***: Duratocin; ***UK***: Pabal; ***Ukr.***: Pabal (Пабал).

Carboprost *(BAN, USAN, rINN)*

Carboprostum; 15-Me-$PGF_{2\alpha}$; Methyldinoprost; (15*S*)-15-Methylprostaglandin $F_{2\alpha}$; U-32921; Карбопрост.

(5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-9,11,15-Trihydroxy-15-methylprosta-5,13-dienoic acid; (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*E*)-(3*S*)-3-hydroxy-3-methyloct-1-enyl]cyclopentyl]hept-5-enoic acid.

$C_{21}H_{36}O_5$=368.5

CAS — 35700-23-3.

ATC — G02AD04.

ATC Vet — QG02AD04.

UNII — 7B5032XT6O.

Carboprost Methyl *(BANM, USAN, rINNM)*

Carboprost Methyle; Carboprostum Methylis; Methyl Carboprost; Metil carboprost; U-36384; Карбопрост Метил.

The methyl ester of carboprost.

$C_{22}H_{38}O_5$=382.5

CAS — 35700-21-1.

ATC — G02AD04.

ATC Vet — QG02AD04.

Pharmacopoeias. In *Chin.*

Carboprost Trometamol *(BANM, rINNM)*

Carboprost Trometamol; Carboprost-Trometamol; Carboprost Tromethamine (USAN); Carboprostum Trometamoli; Carboprostum Trometamolum; Kaboprosttrometamol; Karboprost z trometamolem; Karboprostas trometamolis; Karboprostitrometamoli; Karboprost-trometamol; U-32921E; Карбопрост Трометамол.

$C_{21}H_{36}O_5.C_4H_{11}NO_3$=489.6

CAS — 58551-69-2.

ATC — G02AD04.

ATC Vet — QG02AD04.

UNII — U4526F86FJ.

Description. Carboprost trometamol is a compound of carboprost with trometamol in a ratio of 1:1.

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

Ph. Eur. 8: (Carboprost Trometamol). A white or almost white powder. Soluble in water. Store at a temperature below -15 degrees.

USP 36: (Carboprost Tromethamine). A white to off-white powder. Soluble in water. Store at -25 degrees to -10 degrees.

Uses and Administration

Carboprost is a synthetic 15-methyl analogue of dinoprost (prostaglandin $F_{2\alpha}$; below). It is a uterine stimulant with a more prolonged action than dinoprost; the presence of the methyl group delays inactivation by enzymic dehydrogenation.

Carboprost is used for the termination of pregnancy (p. 2131.3) and for the treatment of refractory postpartum haemorrhage due to uterine atony (p. 2130.2) that is not controlled by oxytocin and ergot preparations. It is usually given intramuscularly as the trometamol salt but doses are expressed in terms of carboprost. Carboprost trometamol 1.3 micrograms is equivalent to about 1 microgram of carboprost.

For the **termination** of second trimester pregnancy (between 13 and 20 weeks of gestation) the equivalent of 250 micrograms of carboprost is given by deep intramuscular injection and repeated every 1½ to 3½ hours depending on the uterine response. If necessary the dose may be increased to 500 micrograms, but the total dose given should not exceed 12 mg, and continuous use for more than 2 days is not recommended. If preferred, a test dose of 100 micrograms may be given initially. Carboprost trometamol has also been given intra-amniotically in a dose equivalent to 1 mg of carboprost over five minutes; this dose may be repeated after 24 hours if termination has not occurred and the membranes are intact. A total dose of 5 mg should not be exceeded.

Carboprost methyl given as vaginal pessaries has been tried for termination of pregnancy in the second trimester.

For the treatment of **postpartum haemorrhage** the equivalent of 250 micrograms of carboprost is given by deep intramuscular injection as the trometamol salt. If necessary, the dose may be repeated at intervals of about 90 minutes; the interval may be reduced if necessary, but should not be less than 15 minutes. A total dose of 2 mg should not be exceeded.

Haemorrhagic cystitis. Carboprost trometamol instilled into the bladder successfully controlled cyclophosphamide-induced haemorrhagic cystitis (p. 772.3) in 15 of 24 bone marrow transplant patients.[1] The dose consisted of 50 mL of solutions containing 2 to 10 micrograms/mL instilled four times daily for 7 days.

1. Ippolito C, *et al.* Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. *Urology* 1995; **46**: 811–15.

Adverse Effects and Precautions

As for Dinoprostone, p. 2134.3 and p. 2136.1, respectively.

Carboprost may cause bronchospasm and, less frequently, dyspnoea and pulmonary oedema. Patients with cardiopulmonary disorders should be monitored for reductions in arterial-oxygen content.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Effects on the fetus. Congenital abnormalities have been reported in pregnancies carried to term after failed termination using prostaglandins, including carboprost (see under Dinoprostone, p. 2135.2).

Effects on the neonate. For a report of inadvertent intramuscular administration of carboprost to a neonate, see under Dinoprostone, p. 2135.2.

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including carboprost, for termination of pregnancy or induction of labour, see Dinoprostone, p. 2135.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carboprost 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 30/07/11)

Interactions

As for Dinoprostone, p. 2136.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Prostin/15M; ***Canad.***: Hemabate; ***China***: Hemabate (欣母沛); Kayun (卡孕); ***Cz.***: Prostin 15M; ***Denm.***: Prostinfenem; ***India***: Deviprost; Prostodin; ***Malaysia***: Hemabate; ***Neth.***: Prostin/15M†; ***NZ***: Prostin 15M; ***Philipp.***: Prostodin; ***Singapore***: Hemabate; ***Swed.***: Prostinfenem; ***UK***: Hemabate; ***USA***: Hemabate.

Pharmacopoeial Preparations

USP 36: Carboprost Tromethamine Injection.

Demoxytocin *(rINN)*

Deamino-oxytocin; Demoksitosiini; Demoxitocina; Démoxytocine; Demoxytocinum; Desaminocitocina; Desaminooxytocin; ODA-914; Демокситоцин.

1-(3-Mercaptopropionic acid)-oxytocin.

$C_{43}H_{65}N_{11}O_{12}S_2$=992.2

CAS — 113-78-0.

ATC — H01BB01.

ATC Vet — QH01BB01.

UNII — 2N9HM3X95F.

Profile

Demoxytocin is a synthetic analogue of oxytocin (p. 2143.1) and has similar properties. It has been given as buccal tablets for the induction and augmentation of labour. It has also been given before nursing to stimulate milk ejection, although it is generally recommended that oxytocics should not be used for this purpose (see p. 2130.1).

Dinoprost *(BAN, USAN, rINN)*

Dinoprostí; Dinoprostum; $PGF_{2\alpha}$; Prostaglandin $F_{2\alpha}$; U-14583; Динопрост.

(5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-9,11,15-Trihydroxyprosta-5,13-dienoic acid; (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid.

$C_{20}H_{34}O_5$=354.5

CAS — 551-11-1.

ATC — G02AD01.

ATC Vet — QG02AD01.

UNII — 87IN85G1HY.

NOTE. In *Martindale* the term dinoprost is used for the exogenous substance and prostaglandin $F_{2\alpha}$ for the endogenous substance.

Pharmacopoeias. In *Jpn.*

Dinoprost Trometamol *(BANM, rINNM)*

Dinoprost Trometamol; Dinoprost Tromethamine (USAN); Dinoprostas trometamolis; Dinoprosttrometamoli; Dinoprosttrometamol; Dinoprost-trometamol; Dinoprostum Trometamoli; Dinoprostum Trometamolum; Dinoproszt-trometamol; $PGF_{2\alpha}$ THAM; Prostaglandin $F_{2\alpha}$ Trometamol; U-14583E; Динопрост Трометамол.

$C_{20}H_{34}O_5.C_4H_{11}NO_3$=475.6

CAS — 38562-01-5.

ATC — G02AD01.

ATC Vet — QG02AD01.

UNII — CT68BQSA68.

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

Ph. Eur. 8: (Dinoprost Trometamol). A white or almost white powder. Very soluble in water; freely soluble in alcohol; practically insoluble in acetonitrile.

USP 36: (Dinoprost Tromethamine). A white to off-white crystalline powder. Very soluble in water; slightly soluble in chloroform; freely soluble in dimethylformamide; soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Dinoprost is a prostaglandin of the F series (p. 2598.1) with actions on smooth muscle; the endogenous substance is termed prostaglandin $F_{2\alpha}$ and is rapidly metabolised in the body. It induces contraction of uterine muscle at any stage of pregnancy and is reported to act mainly as a vasoconstrictor on blood vessels and as a bronchoconstrictor on bronchial muscle.

Dinoprost is used mainly for the termination of pregnancy (p. 2131.3). It may also be used for missed miscarriage, hydatidiform mole, and intra-uterine fetal death. Dinoprost has also been given for the induction of labour but has a higher incidence of adverse effects than dinoprostone, and is no longer routinely recommended; more appropriate treatment is discussed on p. 2129.1.

Dinoprost is usually given intra-amniotically for termination of pregnancy. It has been given intravenously, but with a high incidence of adverse effects. The extra-amniotic route has also been used. Dinoprost is given as the trometamol salt, but doses are described in terms of the base; 1.3 mg of dinoprost trometamol is equivalent to about 1 mg of dinoprost.

For the termination of pregnancy during the second trimester 40 mg of dinoprost is given intra-amniotically by slowly injecting 8 mL of a solution containing 5 mg/mL into the amniotic sac. A further dose of 10 to 40 mg may be given after 24 hours if the termination process has not been established or completed and the membranes are still intact. It should not be given continuously for more than 2 days.

Ileus. Ileus induced by vinca alkaloids in 3 patients with carcinoma of the lung was successfully relieved by the intravenous infusion of dinoprost 300 to 500 nanograms/kg per minute for 2 hours twice daily.[1]

1. Saito H, *et al.* Prostaglandin $F_{2\alpha}$ in the treatment of vinca alkaloid-induced ileus. *Am J Med* 1993; 95: 549–51.

Adverse Effects and Precautions

As for Dinoprostone, below and p. 2136.1, respectively.

Dinoprost can cause bronchoconstriction, and bronchospasm with wheezing and dyspnoea has occurred, especially in asthmatic patients.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Interactions

As for Dinoprostone, p. 2136.1. Alcohol and beta agonists may reduce the efficacy of dinoprost.

For a report of a severe reaction after the use of oxytocin, methylergometrine, and dinoprost, see under Dinoprostone, p. 2136.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Prostin F2 Alpha; *Canad.*: Prostin F2 Alpha; *China*: Enzaprost P (安普诺维); *Cz.*: Enzaprost P; *Gr.*: Enzaprost; Prostin F2; *Hong Kong*: Prostin F2 Alpha; *Hung.*: Enzaprost P; *Israel*: Prostin F2 Alpha; *Jpn*: Prostarmon.F; *NZ*: Prostin F2 Alpha; *Pol.*: Enzaprost; *Rus.*: Enzaprost F (Энзапрост Ф); Prostin F2 Alfa (Простин F2-Альфа); *S. Afr.*: Prostin F2 Alpha; *Ukr.*: Enzaprost F (Энзапрост-Ф).

Dinoprostone *(BAN, USAN, rINN)*

Dinoprostol; Dinoprostona; Dinoprostonas; Dinoprostoni; Dinoprostonum; Dinoproszton; PGE_2; Prostaglandin E_2; U-12062; Динопростон.

(5*Z*,13*E*)-(8*R*,11*R*,12*R*,15*S*)-11,15-Dihydroxy-9-oxoprosta-5,13-dienoic acid; (*Z*)-7-[(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid.

$C_{20}H_{32}O_5$=352.5

CAS — 363-24-6.

ATC — G02AD02.

ATC Vet — QG02AD02.

UNII — K7Q1JQR04M.

NOTE. In *Martindale* the term dinoprostone is used for the exogenous substance and prostaglandin E_2 for the endogenous substance.

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

Ph. Eur. 8: (Dinoprostone). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; freely soluble in alcohol; very soluble in methyl alcohol. Store at a temperature not exceeding -15 degrees.

USP 36: (Dinoprostone). A white to off-white, crystalline powder. Freely soluble in alcohol, in acetone, in dichloromethane, in ether, in ethyl acetate, in isopropyl alcohol, in methyl alcohol; soluble in diisopropyl ether and in toluene; practically insoluble in hexanes. Protect from light.

Uses and Administration

Dinoprostone is a prostaglandin of the E series (p. 2598.1) with actions on smooth muscle; the endogenous substance is termed prostaglandin E_2 and is rapidly metabolised in the body. It induces contraction of uterine muscle at any stage of pregnancy and is reported to act mainly as a vasodilator and as a bronchodilator. Dinoprostone is used mainly in the induction of labour (p. 2129.1); it may also be used for the termination of pregnancy (p. 2131.3), missed miscarriage, hydatidiform mole, and intra-uterine fetal death.

Dinoprostone is usually given vaginally. It may also be given intravenously, extra-amniotically, or orally, but the intravenous route has been associated with a high incidence of adverse effects and is generally only used for missed miscarriage or hydatidiform mole.

For the **induction of labour** dinoprostone is used to ripen (soften and dilate) the cervix before the membranes are ruptured and to induce labour at term. The cervical gel used for cervical ripening contains 500 micrograms in 2.5 mL, whereas the vaginal gel used for induction of labour contains 1 or 2 mg in 2.5 mL; the vaginal gel should not be used in the cervical canal. Pessaries and vaginal inserts are also available; these are not bioequivalent to the gels and their dosage is different.

To soften and dilate the cervix before induction of labour dinoprostone 500 micrograms is given as *cervical gel.* This dose may be repeated after 6 hours if there was no response to the initial dose; in some cases a third dose may be used to a maximum cumulative dose of 1.5 mg in 24 hours.

For induction of labour the dose as *vaginal gel* is 1 mg (or 2 mg in primigravid patients with unfavourable induction features) followed, if necessary, by a further 1 or 2 mg after 6 hours; a total dose of 3 mg (or 4 mg in unfavourable primigravid patients) should not be exceeded. Alternatively a *vaginal pessary* containing 3 mg may be used and this may be followed, if necessary, by a further 3 mg after 6 to 8 hours; a total dose of 6 mg should not be exceeded.

Nonbiodegradable vaginal inserts that contain 10 mg of dinoprostone, and deliver about 300 micrograms/hour, are also available for cervical ripening. The insert should be removed when cervical ripening is complete, or after 12 or 24 hours (depending on the product) if there has been insufficient cervical ripening. The insert should also be removed if regular painful uterine contractions have started, irrespective of cervical change, or when there has been spontaneous rupture of the membranes, or before amniotomy.

Dinoprostone may be given *orally* for the induction of labour. An initial dose of 500 micrograms can be repeated after 1 hour. Subsequent doses are then given at hourly intervals, and may be increased by 500 micrograms if necessary, until an adequate response is achieved. Single doses of 1.5 mg should not be exceeded. The induction should be considered to have failed if regular uterine contractions have not started after 8 hours of treatment. Oral use has, however, generally been replaced by intravaginal dosage since the latter is associated with fewer gastrointestinal adverse effects.

Dinoprostone has been given *intravenously* for the induction of labour but is no longer recommended for routine use by most authorities. A suggested intravenous dosage has been 250 nanograms/minute infused as a solution containing 1.5 micrograms/mL for 30 minutes, the dose being subsequently maintained or increased according to the patient's response. In intra-uterine fetal death higher doses may be required and an initial rate of 500 nanograms/minute has been used with increases at intervals of not less than 1 hour.

For the **termination of pregnancy** 1 mL of a solution containing dinoprostone 100 micrograms/mL may be instilled *extra-amniotically* through a suitable Foley catheter, with subsequent doses of 1 or 2 mL given at intervals usually of 2 hours, according to response. Dinoprostone has also been given *intravenously* for the termination of pregnancy and for missed miscarriage or hydatidiform mole. A solution containing 5 micrograms/mL may be infused at a rate of 2.5 micrograms/minute for 30 minutes, the infusion then being maintained or increased to a rate of 5 micrograms/minute; this rate should be maintained for at least 4 hours before making further increases.

In the USA dinoprostone pessaries are licensed for the termination of second trimester pregnancy. A dose of 20 mg is given *intravaginally* and repeated every 3 to 5 hours according to response for up to 2 days. A total maximum dose of 240 mg has been suggested. Pessaries are also licensed in the USA in missed miscarriage, intra-uterine fetal death, and benign hydatidiform mole.

Dinoprostone is used in some centres to maintain the patency of the ductus arteriosus (see below).

Administration in children. Dinoprostone may be used in infants to maintain the patency of the ductus arteriosus (see below).

Haemorrhagic cystitis. Dinoprostone instilled into the bladder for 4 hours and repeated for 4 days successfully improved severe cyclophosphamide-induced haemorrhagic cystitis (p. 772.3) in a bone marrow transplant recipient.[1] Similar results were obtained in another series of 10 patients.[2] A solution containing 750 micrograms of dinoprostone in 200 mL of sodium chloride 0.9% was used.[1,2]

1. Mohinddin J, *et al.* Treatment of cyclophosphamide-induced cystitis with prostaglandin E_2. *Ann Intern Med* 1984; 101: 142.
2. Laszlo D, *et al.* Prostaglandin E2 bladder instillation for the treatment of hemorrhagic cystitis after allogeneic bone marrow transplantation. *Haematologica* 1995; 80: 421–5.

Hepatic disorders. See under Alprostadil, p. 2352.3, for reference to the use of prostaglandins, including dinoprostone, in the treatment of viral hepatitis.

Patent ductus arteriosus. Prostaglandins, particularly alprostadil (p. 2352.2) and dinoprostone, may be used to maintain the patency of the ductus arteriosus in infants with congenital heart disease until surgery can be performed to correct the malformation. Treatment for a longer period, especially with oral dinoprostone, may facilitate later surgery by allowing growth of the infants and their pulmonary arteries. Beneficial responses to long-term use of dinoprostone have been reported.[1,2] It has been suggested that oral treatment should be continued for up to 4 weeks initially and a decision then made whether to proceed with surgery or to plan a longer course of treatment to encourage further growth. When gastrointestinal absorption is expected to be poor or when oral treatment is ineffective, dinoprostone has been given by intravenous infusion.[1]

Although dinoprostone is not licensed for use in children in the UK, the *BNFC* includes the following doses:

- oral: 20 to 25 micrograms/kg every 1 to 2 hours, doubled if necessary; if treatment continues for more than 1 week then gradually reduce the dose
- intravenous: an initial dose of 5 nanograms/kg per minute increased as necessary, in steps of 5 nanograms/kg per minute, to 20 nanograms/kg per minute; further increases may be needed and doses of up to 100 nanograms/kg per minute have been used, however, these are associated with an increased risk of adverse effects

1. Silove ED, *et al.* Evaluation of oral and low dose intravenous prostaglandin E_2 in management of ductus dependent congenital heart disease. *Arch Dis Child* 1985; 60: 1025–30.
2. Thanopoulos BD, *et al.* Prostaglandin E_2 administration in infants with ductus-dependent cyanotic congenital heart disease. *Eur J Pediatr* 1987; 146: 279–82.

Pemphigus. Erosive oral lesions in 3 patients[1] with pemphigus vulgaris (p. 1687.1), that had previously been refractory to standard corticosteroid therapy, resolved on sucking oral dinoprostone tablets 1.5 to 3 mg daily. Symptoms recurred within weeks of ceasing dinoprostone but could be controlled by courses of 0.5 to 1 mg daily for 1 to 2 weeks, when required. In a group of 10 patients,[2] topical dinoprostone produced similar results in 6 patients, but disease was exacerbated in the others; the dinoprostone was applied twice daily, but details of the dosage form and dose were not reported.

1. Morita H, *et al.* Clinical trial of prostaglandin E_2 on the oral lesions of pemphigus vulgaris. *Br J Dermatol* 1995; 132: 165–6.
2. Kumaran MS, Kanwar AJ. Efficacy of topical PGE2 in recalcitrant oral lesions of pemphigus vulgaris: a clinical trial. *J Eur Acad Dermatol Venereol* 2006; 20: 898–9.

Peripheral vascular disease. Various prostaglandins have been used in the treatment of peripheral vascular disorders (p. 1272.3), particularly in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3), but do not constitute mainline therapy.

Postpartum haemorrhage. Dinoprostone and other prostaglandins have been used to control severe postpartum haemorrhage (p. 2130.2) unresponsive to ergometrine and oxytocin.

Beneficial response to continuous intra-uterine irrigation with dinoprostone solution 1.5 micrograms/mL was seen in 22 patients with postpartum haemorrhage unresponsive to other treatment.[1] Secondary postpartum haemorrhage was controlled in another patient using a dinoprostone 3-mg vaginal pessary held against the uterine wall.[2] A nonbiodegradable dinoprostone vaginal insert has also been tried in the prevention of postpartum blood loss and in one report[3] was as effective as intravenous oxytocin.

1. Peyser MR, Kupfermine MJ. Management of severe postpartum hemorrhage by intrauterine irrigation with prostaglandin E_2. *Am J Obstet Gynecol* 1990; 162: 694–6.
2. Markos AR. Prostaglandin E_2 intrauterine suppositories in the treatment of secondary postpartum hemorrhage. *J R Soc Med* 1989; 82: 504–5.
3. Ozalp E, *et al.* Dinoprostone vaginal insert versus intravenous oxytocin to reduce postpartum blood loss following vaginal or cesarean delivery. *Clin Exp Obstet Gynecol* 2010; 37: 53–5.

Vitiligo. The topical use of dinoprostone has been reported to produce repigmentation in patients with vitiligo (see Pigmentation Disorders, p. 1687.2). In small groups of patients with vitiligo affecting less than 5% of the body-surface, moderate or complete repigmentation occurred in the majority of patients over a treatment period of 6 months.[1,2] The mean onset of effect was seen after 2 months of treatment.[2] In one report a gel containing dinoprostone 166.6 micrograms/g was applied to the affected areas in the evening;[1] in another report a gel containing 250 micrograms/g was applied twice daily.[2] Perilesional hyperpigmentation was seen in many patients, but disappeared after stopping treatment.[1]

1. Parsad D, *et al.* Topical prostaglandin analog (PGE_2) in vitiligo—a preliminary study. *Int J Dermatol* 2002; 41: 942–3.
2. Kapoor R, *et al.* Evaluation of safety and efficacy of topical prostaglandin E_2 in treatment of vitiligo. *Br J Dermatol* 2009; 160: 861–3.

Adverse Effects

The incidence and severity of adverse reactions to dinoprostone are dose-related and also depend to some extent on the route; the intravenous route has been associated with a high incidence of adverse effects. Nausea, vomiting, diarrhoea, and abdominal pain are common by all routes. Back pain and rash can occur. Transient cardiovascular (vasovagal) symptoms have included flushing, shivering, headache, dizziness, and hypotension; there have been rare reports of myocardial infarction and cardiac arrest. Hypertension has also been reported. Convulsions and EEG changes have occurred rarely. Local tissue

irritation and erythema, as well as pyrexia and raised white cell count, may follow intravenous doses but generally revert to normal after termination of the infusion. Transient pyrexia and raised white cell count may also occur after intravaginal use. Local infection may follow intra- or extra-amniotic therapy.

Vaginal bleeding and uterine pain, which are expected with prostaglandin use in the medical termination of pregnancy, may also occur when they are used to soften and dilate the cervix before surgical termination. Excessive uterine activity may occur and there have been occasional reports of uterine rupture after the use of prostaglandins to terminate pregnancy or induce labour; fetal distress and, rarely, fetal death have occurred during induction. There have been cases of anaphylactoid syndrome of pregnancy (amniotic fluid embolism) in women given dinoprostone. Disseminated intravascular coagulation has occurred rarely.

Dinoprostone, although generally acting as a bronchodilator, may cause bronchoconstriction in some individuals. Hypersensitivity reactions have occurred.

Incidence of adverse effects. Adverse effects were evaluated in 626 patients[1] undergoing abortion (usually in the second trimester), using extra-amniotic or intra-amniotic dinoprost or dinoprostone, often with oxytocin. Vomiting occurred in 291, diarrhoea in 28, pyrexia in 34, transient hypotension (fall in systolic blood pressure of at least 20 mmHg) in 25, transient bronchospasm in 2 patients given extra-amniotic dinoprost, and blood loss exceeding 250 mL in 68 (38 lost more than 500 mL). No patients had convulsions even though 8 were being treated for epilepsy. Three patients sustained lacerations to the cervix. Five patients complained of breast soreness or lactation; these symptoms may have been under-reported. Overall 14 patients were re-admitted; 13 because of excessive vaginal bleeding and 1 because of pelvic infection.

A later report describes the cumulative experience in 3313 pregnancies[2] in which dinoprostone gel was used for induction of term labour or cervical ripening. Adverse effects were rare. Vomiting, fever, and diarrhoea occurred in about 0.2% of mothers and were difficult to distinguish from the effects of concurrent drug therapy. Detectable myometrial activity was dose-related and more common after intravaginal than after intracervical use. Myometrial activity was reported in 0.6 to 6% of patients following intravaginal application and hyperstimulation was virtually non-existent at an intracervical dose of 500 micrograms. Fetal effects were negligible in the absence of uterine hyperstimulation.

1. MacKenzie IZ, *et al.* Prostaglandin-induced abortion: assessment of operative complications and early morbidity. *BMJ* 1974; 4: 683–6.
2. Rayburn WF. Prostaglandin E_2 gel for cervical ripening and induction of labor: a critical analysis. *Am J Obstet Gynecol* 1989; 160: 529–34.

Effects on the bones. Reversible periosteal reactions of the long bones and bone thickening have occurred in infants receiving long-term therapy with prostaglandins of the E series (see Alprostadil, p. 2353.2). In addition, reversible widening of cranial sutures was reported[1] in 2 neonates given dinoprostone intravenously for 95 and 97 days respectively.

1. Hoevels-Guerich H, *et al.* Widening of cranial sutures after long-term prostaglandin E_2 therapy in two newborn infants. *J Pediatr* 1984; 105: 72–4.

Effects on the cardiovascular system. Cardiovascular adverse effects are most common after intravenous dinoprostone but may also occur with other routes. Severe cardiovascular disorders reported with the intra-amniotic or intravaginal use of dinoprost or dinoprostone have included: cardiac arrhythmias in 3 patients,[1,2] fatal in 2 of them;[2] hypotension, tachypnoea, and tachycardia in 3 patients[3,4] with associated pyrexias in 2 patients;[3] and fatal myocardial infarction in a patient who had several high-risk factors for ischaemic heart disease.[5]

Severe hypertension occurred in a patient[6] who received dinoprostone by direct myometrial injection and by intravenous infusion concomitantly for postpartum haemorrhage.

Adverse cardiovascular effects have also been reported with other prostaglandins used in gynaecological or obstetric indications (see under Gemeprost, p. 2137.2, and Sulprostone, p. 2145.3).

1. Burt RL, *et al.* Hypokalemia and cardiac arrhythmia associated with prostaglandin-induced abortion. *Obstet Gynecol* 1977; 50: 45S–46S.
2. Cates W, Jordaan HVF. Sudden collapse and death of women obtaining abortions induced with prostaglandin $F_{2\alpha}$. *Am J Obstet Gynecol* 1979; 133: 398–400.
3. Phelan JP, *et al.* Dramatic pyrexic and cardiovascular response to intravaginal prostaglandin E_2. *Am J Obstet Gynecol* 1978; 132: 28–32.
4. Cameron IT, Baird DT. Sudden collapse after intra-amniotic prostaglandin E_2 injection. *Lancet* 1984; ii: 1046.
5. Patterson SP, *et al.* A maternal death associated with prostaglandin E_2. *Obstet Gynecol* 1979; 54: 123–4.
6. Veber B, *et al.* Severe hypertension during postpartum haemorrhage after i.v. administration of prostaglandin E2. *Br J Anaesth* 1992; 68: 623–4.

Effects on the fetus. A woman who failed to abort despite receiving carboprost intravaginally 7 weeks after conception gave birth at 34 weeks of gestation to an infant with hydrocephalus and abnormal digits.[1] There have been reports of 2 infants born, without congenital abnormality, to women who continued with the pregnancy after attempted mid-trimester termination using intravaginal gemeprost.[2,3] However, abnormalities including limb deformities, cleft palate, anencephaly, cerebellar atrophy, and heart malformation were reported in a review[4] of 71 cases of pregnancy that were continued after attempted termination using mifepristone either alone or with a prostaglandin. Of the 8 cases of abnormality that were reported, 7 occurred in the group of 10 women who had been given intravaginal gemeprost. A case of cerebellar agenesis has also been described[5] after a failed medical termination using mifepristone and gemeprost. For abnormalities reported after the failed misuse of misoprostol alone for termination of pregnancy, see p. 2142.2.

For reports of adverse effects on the fetus due to hyperstimulation of the uterus during labour, see under Effects on the Uterus, below.

1. Collins FS, Mahoney MJ. Hydrocephalus and abnormal digits after failed first-trimester prostaglandin abortion attempt. *J Pediatr* 1983; 102: 620–1.
2. Lakasing L, Spencer JAD. Continuation of pregnancy after mid-trimester gemeprost administration. *Br J Obstet Gynaecol* 1999; 106: 1319–20.
3. Rolland P, Sinha A. Continuation of pregnancy after mid-trimester gemeprost administration. *Br J Obstet Gynaecol* 2000; 107: 1184.
4. Sitruk-Ware R, *et al.* Fetal malformation and failed medical termination of pregnancy. *Lancet* 1998; 352: 323.
5. Afadapa FK, Elsapagh K. Isolated one-sided cerebellar agenesis following an attempted medical termination of pregnancy. *J Obstet Gynaecol* 2006; 26: 581–2.

Effects on the gastrointestinal system. Necrotising enterocolitis has been associated with the use of intravenous[1] or oral[2] dinoprostone, or intravenous alprostadil,[2] in infants with symptomatic congenital heart disease. It has been suggested that induced hypotension and apnoea may be responsible,[1] although others[3] did not support this view, or that pulmonary vasodilatation may produce systemic to pulmonary shunting, rendering the gastrointestinal tract relatively ischaemic.[2]

1. Leung MP, *et al.* Necrotizing enterocolitis in neonates with symptomatic congenital heart disease. *J Pediatr* 1988; 113: 1044–6.
2. Singh GK, *et al.* Study of low dosage prostaglandin—usages and complications. *Ther Heart J* 1994; 15: 377–81.
3. Miller MJS, Clark DA. Congenital heart disease and necrotizing enterocolitis. *J Pediatr* 1989; 115: 335–6.

Effects on the neonate. Aspiration of the undissolved remnants of a dinoprostone vaginal tablet caused neonatal respiratory distress due to mechanical obstruction of the airways; there was no evidence to suggest absorption of dinoprostone from the tablet matrix.[1]

Inadvertent intramuscular injection of carboprost 250 micrograms caused hypertension, bronchospasm, diarrhoea, and hyperthermia in a neonate. There was also an adverse neurological effect that was either a dystonic reaction or seizure activity. The neonate was treated symptomatically and discharged 24 hours later; neurological and developmental examinations were normal at 3 months of age.[2] The authors of this report also learned of 2 other cases that had been reported to the manufacturer, in which neonates given injections of 125 micrograms and 63 micrograms remained asymptomatic.

1. Andersson S, *et al.* Neonatal respiratory distress caused by aspiration of a vaginal tablet containing prostaglandin. *BMJ* 1987; 295: 25–6.
2. Mrvos R, *et al.* Carboprost exposure in a newborn with recovery. *J Toxicol Clin Toxicol* 1999; 37: 865–7.

Effects on the nervous system. Convulsions and EEG changes have been occasionally reported during the use of prostaglandins for termination of pregnancy. Convulsions occurred[1] in 5 of 320 women after intra-amniotic dinoprost, but in other large series[2-4] of patients given dinoprost or dinoprostone by various routes no problems occurred despite the inclusion of patients with a history of epilepsy. However, convulsions were reported[5] in 3 of 4 epileptic patients given sulprostone intramuscularly.

1. Lyncham RC, *et al.* Convulsions and electroencephalogram abnormalities after intra-amniotic prostaglandin $F_{2\alpha}$. *Lancet* 1973; ii: 1003–5.
2. MacKenzie IZ, *et al.* Convulsions and prostaglandin-induced abortion. *Lancet* 1973; ii: 1323.
3. Thiery M, *et al.* Prostaglandins and convulsions. *Lancet* 1974; i: 218.
4. Fraser IS, Gray C. Electroencephalogram changes after prostaglandin. *Lancet* 1974; i: 360.
5. Brandenburg H, *et al.* Convulsions in epileptic women after administration of prostaglandin E_2 derivative. *Lancet* 1990; 336: 1138.

Effects on the uterus. Use of prostaglandins to induce labour or to terminate pregnancy is associated with an increased risk of hyperstimulation of the uterus. Uterine rupture has occurred with carboprost,[1] dinoprost or dinoprostone,[2-7] gemeprost,[8-10] misoprostol,[11-14] and sulprostone.[15-17] These effects have been reported with parenteral, local, and oral dosage. The risk of rupture and associated complications is increased in grand multiparae[4] and those with uterine scarring from previous caesarean section.[5,7] Studies have reported relative risks of between 6 and 10 times those of spontaneous labour after labour induction with dinoprostone in the latter group.[5,7] In addition to rupture, with the risk of potentially fatal maternal haemorrhage, hyperstimulation has been associated with fetal distress and death,[18-20] and maternal death due to anaphylactoid syndrome of pregnancy (amniotic fluid embolism).[18,21]

1. Vergote I, *et al.* Uterine rupture due to 15-methyl prostaglandin $F_{2\alpha}$. *Lancet* 1982; ii: 1402.
2. Claman P, *et al.* Uterine rupture with the use of vaginal prostaglandin E_2 for induction of labor. *Am J Obstet Gynecol* 1984; 150: 889–90.
3. Keller F, Joyce TH. Uterine rupture associated with the use of vaginal prostaglandin E_2 suppositories. *Can Anaesth Soc J* 1984; 31: 80–2.
4. Larsen JV, *et al.* Uterine hyperstimulation and rupture after induction of labour with prostaglandin E_2. *S Afr Med J* 1984; 65: 615–16.
5. Ravasia DJ, *et al.* Uterine rupture during induced trial of labor among women with previous cesarean delivery. *Am J Obstet Gynecol* 2000; 183: 1176–9.
6. Rabl M, *et al.* A randomized trial of vaginal prostaglandin E_2 for induction of labor: insert vs tablet. *J Reprod Med* 2002; 47: 115–19.
7. Taylor DR, *et al.* Uterine rupture with the use of PGE_2 vaginal inserts for labor induction in women with previous cesarean sections. *J Reprod Med* 2002; 47: 549–54.
8. Thavarasah AS, Achanna KS. Uterine rupture with the use of Cervagem (prostaglandin E1) for induction of labour on account of intrauterine death. *Singapore Med J* 1988; 29: 351–2.
9. Byrne P, Onyekwuluje T. Uterine rupture after termination of pregnancy with gemeprost. *BMJ* 1991; 302: 852.
10. Vine SJ, *et al.* Transverse posterior cervicoisthmic rupture after gemeprost pessaries for termination. *BMJ* 1992; 305: 1332.
11. Blanchette HA, *et al.* Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E_1) with those of dinoprostone (prostaglandin E_2) for cervical ripening and induction of labor in a community hospital. *Am J Obstet Gynecol* 1999; 180: 1551–9.
12. Mathews JE, *et al.* Uterine rupture in a multiparous woman during labor induction with oral misoprostol. *Int J Gynaecol Obstet* 2000; 68: 43–4.
13. Khabbaz AY, *et al.* Rupture of an unscarred uterus with misoprostol induction: case report and review of the literature. *J Matern Fetal Med* 2001; 10: 141–5.
14. Nayki U, *et al.* Uterine rupture during second trimester abortion with misoprostol. *Fetal Diagn Ther* 2005; 20: 469–71.
15. Larue L, *et al.* Rupture d'un utérus sain lors d'une interruption de grossesse par prostaglandines au deuxième trimestre. *J Gynecol Obstet Biol Reprod (Paris)* 1991; 20: 269–72.
16. Prasad RNV, Ratnam SS. Uterine rupture after induction of labour for intrauterine death using the prostaglandin E_2 analogue sulprostone. *Aust N Z J Obstet Gynaecol* 1992; 32: 282–3.
17. de Boer MA, *et al.* Low dose sulprosone for termination of second and third trimester pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2001; 99: 244–8.
18. Stronge J, *et al.* A neonatal and maternal death following the administration of intravaginal prostaglandin. *J Obstet Gynaecol* 1987; 7: 271–2.
19. Quinn MA, Murphy AJ. Fetal death following extra-amniotic prostaglandin gel: report of two cases. *Br J Obstet Gynaecol* 1981; 88: 650–1.
20. Simmons K, Savage W. Neonatal death associated with induction of labour with intravaginal prostaglandin E_2: case report. *Br J Obstet Gynaecol* 1984; 91: 598–9.
21. Less A, *et al.* Vaginal prostaglandin E_2 and fatal amniotic fluid embolus. *JAMA* 1990; 263: 3259–60.

Overdosage. Severe adverse effects associated with intra-amniotic prostaglandins have been attributed to absorption into the systemic circulation of doses higher than would normally be given systemically. Rigors, vomiting, severe abdominal pain, and an intense desire to urinate and defaecate occurred[1] in 3 patients given dinoprostone intra-amniotically for mid-trimester abortion; one patient had peripheral vasoconstriction and a rapid low-volume pulse, with hypotension, and another had peripheral cyanosis. It was suggested[2] that this might have been due to displacement of the needle or cannula outside the amniotic sac. In 2 of the patients prior use of urea may have increased the rate of absorption of prostaglandins from the amniotic cavity. In a further report[3] flushing, severe headache, and nausea immediately after a test dose of dinoprost 2.5 mg was also thought to be due to incorrect positioning of the needle and consequent injection into the systemic circulation; at least part of the dose might have been injected into the peritoneal cavity.[4]

Severe reactions have also been reported with prostaglandins given to abort hydatidiform moles. A 20-year-old woman given 20 mg of dinoprostone by injection into the uterine cavity developed profound hypotension, bradycardia, and rigors, followed by nausea, vomiting, suprapubic pain, an increased pulse rate, pyrexia, and generalised flushing.[5] Since there are no fetal membranes in a molar pregnancy, intra-uterine administration is similar to extra-amniotic administration and the dose used was 100 times higher than the usual extra-amniotic dose.[4] However, in a similar patient[6] 'extra-amniotic' instillation of dinoprostone 200 micrograms was followed immediately by nausea, retching, severe abdominal pain, dizziness, difficulty in breathing and the production of frothy blood-stained sputum, an imperceptible pulse, and hypotension; the dinoprostone had probably been injected directly into the maternal circulation.

1. Ross AH, Whitehouse WL. Adverse reactions to intra-amniotic urea and prostaglandin. *BMJ* 1974; 1: 642.
2. Craft I, Bowen-Simpkins P. Adverse reactions to intra-amniotic urea and prostaglandin. *BMJ* 1974; 2: 446.
3. Brown R. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; 2: 382.
4. Karim SMM. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; 3: 347.

The symbol † denotes a preparation no longer actively marketed

5. Smith AM. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; 2: 382–3.
6. McNicol E, Gray H. Adverse reaction to extra-amniotic prostaglandin E_2. *Br J Obstet Gynaecol* 1977; 84: 229–30.

Precautions

Dinoprostone should not be given to patients in whom oxytocic drugs are generally contra-indicated because spontaneous labour or vaginal delivery are liable to harm either the mother or the fetus (see also Oxytocin, p. 2144.2). This includes significant cephalopelvic disproportion or unfavourable presentation of the fetus, placenta praevia, or fetal distress. It should not be used where there is a predisposition to uterine rupture, as in high parity or the presence of a uterine scar from previous caesarean section or major uterine surgery, or in those with a history of pelvic inflammatory disease. Since prostaglandins enhance the effects of oxytocin, use of these drugs together or in sequence should be carefully monitored.

Dinoprostone is contra-indicated in active cardiac, pulmonary, renal, or hepatic disease. It should be used with caution in patients with glaucoma or raised intra-ocular pressure, a history of asthma or epilepsy, hepatic or renal impairment, or cardiovascular disease.

In the induction of labour cephalopelvic relationships should be carefully evaluated before use. During use uterine activity, fetal status, and the progress of cervical dilatation should be carefully monitored to detect adverse responses, such as hypertonus, sustained uterine contractions, or fetal distress. In patients with a history of hypertonic uterine contractility or tetanic uterine contractions, uterine activity and the state of the fetus should be continuously monitored throughout labour. Where high-tone myometrial contractions are sustained the possibility of uterine rupture should be considered.

Dinoprostone should not be given by the myometrial route, since there is a possible association with cardiac arrest in severely ill patients. The extra-amniotic route should not be used in patients with cervicitis or vaginal infections. Vaginal preparations of dinoprostone are not recommended in the induction of labour once the membranes are ruptured, because information about use in this group is limited. In some countries, intravenous prostaglandins are considered to be contra-indicated in women who smoke.

Dinoprostone should be used with caution in women who have conditions that could further increase the risk of postpartum disseminated intravascular coagulation, which is associated with pharmacologically induced labour. This includes women with gestational diabetes, hypertension, or hypothyroidism. Women over 30 years of age and those past the fortieth week of pregnancy are also at increased risk.

In the therapeutic termination of pregnancy, fetal damage has been seen in cases of incomplete termination and the appropriate treatment for complete evacuation of the uterus should therefore be instituted whenever termination is unsuccessful or incomplete. Dinoprostone should not be used for termination in patients with pelvic infection, unless adequate treatment has already been started.

Administration. For the hazards of unintentional systemic absorption of prostaglandins after intra-uterine use for the termination of pregnancy and abortion of hydatidiform moles, see Overdosage in Adverse Effects, p. 2135.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dinoprostone 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 30/07/11)

Interactions

Dinoprostone enhances the effects of oxytocin on the uterus. There is a theoretical risk that prostaglandin synthetase inhibitors, such as aspirin and NSAIDs, might alter the efficacy of dinoprostone.

Uterine stimulants. Marked hypertension, vomiting, and severe dyspnoea occurred after the sequential use of *oxytocin, methylergometrine,* and *dinoprost* within the space of 10 minutes to a woman with postpartum haemorrhage.[1]

1. *Cohen S, et al.* Severe systemic reactions following administration of different ureotonic [uterotonic] drugs. *N Y State J Med* 1983; 83: 1060–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Prolisina E2; Propess; *Austral.*: Cervidil; Prostin E2; *Austria*: Prepidil; Propess; Prostin E2; *Belg.*: Prepidil; Propess; Prostin E2; *Braz.*: Propess; *Canad.*: Cervidil; Prepidil; Prostin E2; *Cz.*: Prepidil; Propess†; Prostin E2; *Denm.*: Minprostin; Propess; Prostin E2; *Fin.*: Minprostin†; Propess†; *Fr.*: Prepidil; Propess; Prostine E_2; *Ger.*: Minprostin E_2; Prepidil; Propess; *Gr.*: Minprostin; Prepidil; Propess; Prostin E2; *Hong Kong*: Prostin E2; *Hung.*: Prepidil; Prostin E2; *India*: Cerviprime; Dinoripe; Primiprost; *Indon.*: Prostin E2†; *Irl.*: Prostin E2; *Israel*: Prepidil; Propess; Prostin E2; *Ital.*: Prepidil; Propess; Prostin E2; *Malaysia*: Prostin E2; *Mex.*: Prepidil; Propess; *Neth.*: Prepidil; Propess; Prostin E2; *Norw.*: Minprostin; *NZ*: Cervidil; Prostin E2; *Philipp.*: Cerviprime; *Pol.*: Prepidil; Propess; *Port.*: Propess; Prostin E2; *Rus.*: Prepidil (Препидил); Prostenongel (Простенонгель); Prostin E2 (Простин Е2); *S.Afr.*: Prandin E_2; Prepidil; Propess; Prostin E2; *Singapore*: Prostin E2; *Spain*: Prepidil; Propess; *Swed.*: Minprostin; Propess; *Switz.*: Propess; Prostin E2; *Thai.*: Prostin E2; *UK*: Propess; Prostin E2; *Ukr.*: Cervistin (Цервистин); *USA*: Cervidil; Prepidil; Prostin E2.

Pharmacopoeial Preparations
BP 2014: Dinoprostone Oral Solution.

Ergometrine Maleate *(BANM, rINNM)*

Ergobasine Maleate; Ergometriinimaleaatti; Ergometrina, maleato de; Ergométrine, Maléate d'; Ergometrinhydrogenmaleat; Ergometrini Maleas; Ergometrinmaleat; Ergometrinmaleát; Ergometrin-maleinát; Ergometrino maleatas; Ergonovine Bimaleate; Ergonovine Maleate; Ergostetrine Maleate; Ergotocine Maleate; Maleato de ergobasina; Maleato de ergometrina; Maleato de Ergonovina; Эрометрина Малеат.

N-[(*S*)-2-Hydroxy-1-methylethyl]-D-lysergamide hydrogen maleate; 9,10-Didehydro-*N*-[(*S*)-2-hydroxy-1-methylethyl]-6-methylergoline-8β-carboxamide hydrogen maleate.

$C_{19}H_{23}N_3O_2.C_4H_4O_4$=441.5

CAS — 60-79-7 (ergometrine); 129-51-1 (ergometrine maleate).

ATC — G02AB03.

ATC Vet — QG02AB03.

UNII — YMH3D0ZJWV.

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

Ph. Eur. 8: (Ergometrine Maleate). A white or almost white or slightly coloured, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 3.6 to 4.4. Store in airtight glass containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Ergonovine Maleate). A white to greyish-white or faintly yellow, odourless, microcrystalline powder. It darkens with age and on exposure to light. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Stability. Deterioration and degradation of ergometrine-containing injections has been seen when exposed to high temperatures in the tropics.[1–4] The mean loss in one study[3] of ergometrine injection under shipment to the tropics was 5.8%, but in some individual samples the loss was more marked: 18 of 80 test samples contained less than 80% of the stated content, and in 3 cases the content was less than 60%. A similar but much less significant pattern was seen with methylergometrine: the content varied from 98.6 to 99.5% of the labelled amount. Tablets of ergometrine and methylergometrine were also shown to be unstable under simulated tropical conditions, with humidity as the main adverse factor.[5]

1. Walker GJA, *et al.* Potency of ergometrine in tropical countries. *Lancet* 1988; ii: 393.
2. Abu-Reid IO, *et al.* Stability of drugs in the tropics. *Int Pharm J* 1990; 4: 6–10.
3. Hogerzeil HV, *et al.* Stability of essential drugs during shipment to the tropics. *BMJ* 1992; 304: 210–12.
4. Hogerzeil HV, Walker GJ. Instability of (methyl)ergometrine in tropical climates: an overview. *Eur J Obstet Gynecol Reprod Biol* 1996; 69: 25–9.
5. de Groot ANJA, *et al.* Ergometrine and methylergometrine tablets are not stable under simulated tropical conditions. *J Clin Pharm Ther* 1995; 20: 109–13.

Uses and Administration

Ergometrine has a much more powerful action on the uterus than most other ergot alkaloids, especially on the puerperal uterus. Its main action is the production of intense contractions, which at higher doses are sustained, in contrast to the more physiological rhythmic uterine contractions induced by oxytocin; its action is more prolonged than that of oxytocin.

Ergometrine maleate is used in the active management of the third stage of labour, and to prevent or treat postpartum or postabortal haemorrhage (p. 2130.2) caused by uterine atony; by maintaining uterine contraction and tone, blood vessels in the uterine wall are compressed, and blood flow reduced.

In the **active management of the third stage of labour**, ergometrine maleate and oxytocin are given together under full obstetric supervision. A dose of ergometrine maleate 500 micrograms and oxytocin 5 units (as the fixed combination *Syntometrine*) is injected intramuscularly after delivery of the anterior shoulder, or, at the latest, immediately after delivery of the infant; contractions are reported to occur within 2 to 7 minutes. Delivery of the placenta is actively assisted while the uterus is firmly contracted.

In the prevention or treatment of **postpartum haemorrhage**, ergometrine maleate may be used alone, usually in an intramuscular dose of 200 to 500 micrograms. In emergencies such as excessive uterine bleeding, a dose of 250 to 500 micrograms has been given intravenously. Intravenous doses should be given over at least 1 minute to reduce the risk of adverse effects, particularly hypertension. An intramuscular dose of 200 micrograms has also been used for the prevention or treatment of postabortal haemorrhage. Parenteral treatment of haemorrhage may be followed by ergometrine maleate 200 to 400 micrograms orally 2 to 4 times daily until the danger of atony and haemorrhage has passed, which is usually 48 hours. Tablets have also been given sublingually. The combination preparation *Syntometrine* has been used intramuscularly to prevent or treat postpartum haemorrhage; the *BNF* states that it can also be used in the management of incomplete abortion, usually when surgical evacuation of the uterus is delayed.

In the treatment of mild secondary postpartum haemorrhage, ergometrine maleate has been given orally.

Ergometrine tartrate was formerly used.

Diagnosis and testing. Ergometrine maleate[1–8] or methylergometrine maleate[9,10] have been used in a provocation test for the diagnosis of Prinzmetal's angina (variant angina) (p. 1254.3).

1. Waters DD, *et al.* Ergonovine testing in a coronary care unit. *Am J Cardiol* 1980; 46: 922–30.
2. Health and Public Policy Committee, American College of Physicians. Performance of ergonovine provocative testing for coronary artery spasm. *Ann Intern Med* 1984; 100: 151–2.
3. Song J-K, *et al.* Safety and clinical impact of ergonovine stress echocardiography for diagnosis of coronary vasospasm. *J Am Coll Cardiol* 2000; 35: 1850–6.
4. Kashima K, *et al.* Long-term outcome of patients with ergonovine induced coronary constriction not associated with ischemic electrocardiographic changes. *J Cardiol* 2001; 37: 301–8.
5. Palinkas A, *et al.* Safety of ergot stress echocardiography for non-invasive detection of coronary vasospasm. *Coron Artery Dis* 2001; 12: 649–54.
6. Song JK, *et al.* Prognostic implication of ergonovine echocardiography in patients with near normal coronary angiogram or negative stress test for significant fixed stenosis. *J Am Soc Echocardiogr* 2002; 15: 1346–52.
7. Sueda S, *et al.* Clinical impact of selective spasm provocation tests: comparisons between acetylcholine and ergonovine in 1508 examinations. *Coron Artery Dis* 2004; 15: 491–7.
8. Coma-Canella I, *et al.* Ergonovine test in angina with normal coronary arteries: is it worth doing it? *Int J Cardiol* 2006; 107: 200–6.
9. Bertrand ME, *et al.* Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. *Circulation* 1982; 65: 1299–1306.
10. Lablanche JM, *et al.* Réflexions d'un comité d'experts de la Société française de cardiologie concernant l'usage du maléate de méthylergométrine (Methergin) dans la détection d'une vasomotricité coronaire anormale. *Arch Mal Coeur Vaiss* 1995; 88: 247–53.

Adverse Effects and Treatment

Nausea and vomiting, abdominal pain, diarrhoea, headache, dizziness, tinnitus, chest pain, palpitations, bradycardia and other cardiac arrhythmias, coronary artery vasospasm, myocardial infarction, dyspnoea, and pulmonary oedema have been reported after use of ergometrine. Hypertension may occur, particularly after rapid intravenous dosage; hypotension has also been reported. Hypersensitivity reactions, including shock, have occurred. Ergometrine shows less tendency to produce gangrene than ergotamine, but ergotism has been reported and symptoms of acute poisoning are similar (see p. 674.2).

Adverse effects should be treated as for ergotamine, p. 674.3.

Effects on the respiratory system. Bronchospasm has been reported after use of ergometrine.[1] Although studies *in vitro* on *canine* bronchi have suggested a direct action on smooth muscle, this could not be confirmed in studies using human bronchi.

1. Hill H, *et al.* Ergometrine and bronchospasm. *Anaesthesia* 1987; 42: 1115–16.

Overdosage. Ergometrine maleate has been given accidentally in adult doses to neonates,[1–5] sometimes instead of vitamin K. Symptoms have included peripheral vasoconstriction, encephalopathy, convulsions, respiratory failure, acute renal failure, and temporary lactose intolerance. When given with oxytocin, water intoxication has also been reported.[1] In all of these cases, recovery occurred after intensive symptomatic treatment including assisted ventilation and anticonvulsants. However, deaths have also been recorded.[5] The long-term outcome of ergometrine overdosage has been reported for 6 infants.[5] Their ages at follow-up ranged from 18 months to 5 years; all had normal physical and behavioural development and neurological outcomes.

1. Whitfield MF, Salfield SAW. Accidental administration of Syntometrine in adult dosage to the newborn. *Arch Dis Child* 1980; 55: 68–70.
2. Pandey SK, Haines CL. Accidental administration of ergometrine to newborn infant. *BMJ* 1982; 285: 693.
3. Mitchell AA, *et al.* Accidental administration of ergonovine to a newborn. *JAMA* 1983; 250: 730–1.

4. Donatini B, *et al.* Inadvertent administration of uterotonics to neonates. *Lancet* 1993; 341: 839–40.
5. Dargaville PA, Campbell NT. Overdose of ergometrine in the newborn infant: acute symptomatology and long-term outcome. *J Paediatr Child Health* 1998; 34: 83–9.

Precautions

As for Ergotamine Tartrate, p. 675.1. Ergometrine should also be used with caution in patients with veno-atrial shunts or mitral valve stenosis. Ergometrine is contra-indicated for the induction of labour or for use during the first stage of labour. If used at the end of the second stage of labour, before delivery of the placenta, there must be expert obstetric supervision. Its use should be avoided in patients with pre-eclampsia, eclampsia, or threatened miscarriage.

Interactions

As for Ergotamine Tartrate, p. 675.2. Halothane has been considered to diminish the effects of ergometrine on the uterus.

Sympathomimetics. Use of *dopamine* in a patient treated with ergometrine was associated with subsequent development of gangrene in both hands and feet.[1] In another case,[2] the use of ergometrine with *noradrenaline* resulted in cyanosis of the hands and necrosis in some of the fingers.

1. Buchanan N, *et al.* Symmetrical gangrene of the extremities associated with the use of dopamine subsequent to ergometrine administration. *Intensive Care Med* 1977; 3: 55–6.
2. Chuang S-S. Finger ischemia secondary to the synergistic agonist effect of norepinephrine and ergonovine and in a burn patient. *Burns* 2003; 29: 92–4.

Pharmacokinetics

Ergometrine is reported to be rapidly absorbed after oral doses or intramuscular injection, with onset of uterine contractions in about 5 to 15 minutes and 2 to 7 minutes, respectively. Elimination appears to be mainly by hepatic metabolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Evina; Metrergina; *Gr.*: Mitrotan; Novergo; *India*: Ergotab; Ergotaur; Erinmet; *Mex.*: Ergotrate; *Thai.*: Gynaemine; *USA*: Ergotrate†.

Multi-ingredient Preparations. *Austral.*: Syntometrine; *Hong Kong*: Syntometrine; *Irl.*: Syntometrine; *Malaysia*: Syntometrine; *NZ*: Syntometrine; *S.Afr.*: Syntometrine; *Singapore*: Syntometrine; *UK*: Syntometrine.

Pharmacopoeial Preparations
BP 2014: Ergometrine and Oxytocin Injection; Ergometrine Injection; Ergometrine Tablets;
USP 36: Ergonovine Maleate Injection; Ergonovine Maleate Tablets.

Ergot

Cornezuelo del centeno; Secale Cornutum; Sporysz; Спорынья.
UNII — 01G9XEA93N.

Description. Ergot consists of the sclerotium of the fungus *Claviceps purpurea* (Hypocreaceae) developed in the ovary of the rye, *Secale cereale* (Gramineae). It contains not less than 0.15% of total alkaloids, calculated as ergotoxine, and not less than 0.01% of water-soluble alkaloids, calculated as ergometrine. Some authorities have expressed alkaloidal content in terms of ergotamine and ergometrine.

Uses and Administration

Ergot has the vasoconstricting and oxytocic actions of its constituent alkaloids, especially ergotamine (p. 674.1) and ergometrine (p. 2136.2). A liquid extract or tablets of prepared ergot were formerly used as an oxytocic. Preparations containing ergot extracts have been promoted for use in dyspepsia and nervous disorders.

Adverse Effects and Treatment

As for Ergotamine Tartrate, p. 674.2.

Epidemic ergot poisoning, arising from the ingestion of ergotised rye bread, is now seldom seen. Two forms of epidemic toxicity, which rarely occur together, have been described: a gangrenous form characterised by agonising pain of the extremities of the body followed by dry gangrene of the peripheral parts, and a rarer nervous type giving rise to paroxysmal epileptiform convulsions.

Poisoning. A report of an outbreak of ergotism, attributed to the ingestion of infected wild oats (*Avena abyssinica*), in Ethiopia.[1]

1. King B. Outbreak of ergotism in Wollo, Ethiopia. *Lancet* 1979; ii: 1411.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Iris Med Complex; Nux Med Complex; Secale Med Complex; *Canad.*: Insomnia Passiflora†; PMS; *Fr.*: Amanita Complexe No 75; Aurum Complexe No 38†; Cimicifuga Complexe No 21†; Hypericum Complexe No 26; Kalium Iodatum Complexe No 84†; L 25; L 28; Passiflora GHL; Sclerocalcine; *Ger.*: Aderplus spezial Dr Hagedorn†; Aleuris Oligoplex†; Arte-cyl Ho-Len-Complex; Cefadybasin SE†; Cefakliman S; Elana†; Flenin; metaginkgo†; Migrane Hevert†; Migrane Hevert; Reproven N; Secale-Gastreu; Secalosan N; Vasa-Gastreu N R63; Vertigo-Hevert; *Neth.*: Aesculus Comp; Emvita 11; Emvita 6; Homeocare Vasco; *Rus.*: Ruta-Plus (Рута-Плюс); *Switz.*: metaginkgo; *Ukr.*: Arsenic Comp Iov-Diabet (Арсеник Комп Иов-Диабет).

Ergotoxine

Ecboline; Ergotoxina; Эрготоксин.
CAS — 8006-25-5 (ergotoxine); 8047-28-7 (ergotoxine esilate); 8047-29-8 (ergotaxine phosphate); 564-36-3 (ergocornine); 511-08-0 (ergocristine); 511-09-1 (α-ergocryptine); 20315-46-2 (β-ergocryptine).

Profile

Ergotoxine is a mixture of naturally occurring ergot alkaloids. It contains equal proportions of:

- ergocornine ($C_{31}H_{39}N_5O_5$ = 561.7)
- ergocristine ($C_{35}H_{39}N_5O_5$ = 609.7)
- ergocryptine ($C_{32}H_{41}N_5O_5$ = 575.7) as the α- and β-isomers

Ergotoxine esilate was formerly used as an oxytocic and in the treatment of migraine. The phosphate has also been used.

Gemeprost *(BAN, USAN, rINN)*

16,16-Dimethyl-*trans*-Δ²-prostaglandin E_1 methyl ester; Gémépróst; Gemeprosti; Gemeprostum; ONO-802; SC-37681; Гемепрост.
Methyl (2*E*,13*E*)-(8*R*,11*R*,12*R*,15*R*)-11,15-dihydroxy-16,16-dimethyl-9-oxoprosta-2,13-dienoate; Methyl (*E*)-7-{(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4,4-dimethyloct-1-enyl]-5-oxocyclopentyl}hept-2-enoate.
$C_{23}H_{38}O_5$=394.6
CAS — 64318-79-2.
ATC — G02AD03.
ATC Vet — QG02AD03.
UNII — 45KZB1FOLS.

Uses and Administration

Gemeprost is a synthetic analogue of alprostadil (prostaglandin E_1; p. 2352.2) that is used in the termination of pregnancy (p. 2131.3). In the first trimester, a pessary containing gemeprost 1 mg is inserted into the vagina 3 hours before surgery to soften and dilate the cervix. Gemeprost may also be used for medical termination of pregnancy in the second trimester when a 1-mg pessary is inserted every 3 hours to a maximum of 5 pessaries. If this is ineffective, one further course may be given starting 24 hours after the beginning of the first course. If termination is not well established after 10 pessaries, alternative treatment should be used to complete uterine evacuation. In the case of intra-uterine fetal death in the second trimester, only one course of up to 5 pessaries should be given. Vaginal gemeprost is also used after oral mifepristone (p. 2138.2) in the termination of pregnancy.

Adverse Effects and Precautions

As for Dinoprostone, p. 2134.3 and p. 2136.1, respectively. Pulse and blood pressure should be monitored in patients given gemeprost.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Incidence of adverse effects. The incidence of vomiting (19% or 35%) and diarrhoea (12% or 19%) in 2 studies of patients treated with gemeprost pessaries was similar to that seen with other prostaglandins, but gemeprost was reported to cause less uterine pain.[1,2]

1. Cameron IT, Baird DT. The use of 16,16-dimethyl-trans-Δ² prostaglandin E_1 methyl ester (gemeprost) vaginal pessaries for the termination of pregnancy in the early second trimester: a comparison with extra-amniotic prostaglandin E_2. *Br J Obstet Gynaecol* 1984; 91: 1136–40.
2. Andersen LF, *et al.* Termination of second trimester pregnancy with gemeprost vaginal pessaries and intra-amniotic $PGF_{2\alpha}$: a comparative study. *Eur J Obstet Gynecol Reprod Biol* 1989; 31: 1–7.

Effects on the cardiovascular system. Periods of ventricular standstill of up to 6 seconds were seen in a patient during treatment with gemeprost vaginal pessaries.[1] The patient required temporary cardiac pacing, but no persistent cardiac rhythm disturbances were detected on follow-up. Severe cardiogenic shock due to vasospasm, and subsequent stroke, has been reported in a patient who had received gemeprost pessaries some hours earlier; myocardial infarction ensuing from coronary spasm was reported in a second patient.[2]

1. Kalra PA, *et al.* Cardiac standstill induced by prostaglandin pessaries. *Lancet* 1989; i: 1460–1.
2. Schulze-Sasse U. Life threatening myocardial ischaemia associated with the use of prostaglandin E_1 to induce abortion. *Br J Obstet Gynaecol* 2000; 107: 700–2.

Effects on the fetus. Congenital abnormalities have been reported in pregnancies carried to term after failed termination using prostaglandins, including gemeprost (see under Dinoprostone, p. 2135.2).

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including gemeprost, for termination of pregnancy or induction of labour, see under Dinoprostone, p. 2135.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gemeprost 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 30/07/11)

Interactions

As for Dinoprostone, p. 2136.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Cervagem; *Fr.*: Cervagem; *Ger.*: Cergem; *Ital.*: Cervidil; *Jpn*: Preglandin; *Malaysia*: Cervagem; *NZ*: Cervagem†; *Singapore*: Cervagem; *Swed.*: Cervagem; *UK*: Cervagem.

Methylergometrine Maleate *(BANM, rINNM)*

Maleato de metilergometrina; Methylergobasine Maleate; Méthylergométrine, hydrogénomaléate de; Méthylergométrine, Maléate de; Methylergometrini hydrogenomaleas; Methylergometrini Maleas; Methylergometrinmaleat; Methylergonovine Maleate; Metilergobazin Maleat; Metilergometrin Maleat; Metilergometrina, maleato de; Метилэрометрина Малеат.
N-[(*S*)-1-(Hydroxymethyl)propyl]-D-lysergamide hydrogen maleate; 9,10-Didehydro-*N*-[(*S*)-1-(hydroxymethyl)propyl]-6-methylergoline-8β-carboxamide hydrogen maleate.
$C_{20}H_{25}N_3O_2C_4H_4O_4$=455.5
CAS — 113-42-8 (methylergometrine); 57432-61-8 (methylergometrine maleate).
ATC — G02AB01.
ATC Vet — QG02AB01.
UNII — IR84JPZ1RK.

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

Ph. Eur. 8: (Methylergometrine Maleate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; slightly soluble in anhydrous alcohol. pH of a 0.5% solution is 4.4 to 5.2. Store in airtight containers. Protect from light.

USP 36: (Methylergonovine Maleate). A white to pinkish-tan, odourless, microcrystalline powder. Soluble 1 in 100 of water, 1 in 175 of alcohol, 1 in 1900 of chloroform, and 1 in 8400 of ether. pH of a 0.02% solution in water is between 4.4 and 5.2. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Stability. For mention of slight variations in the methylergometrine content of the injection after transport to a tropical climate, see under Ergometrine Maleate, p. 2136.2.

Uses and Administration

Methylergometrine maleate has an action on the uterus similar to that of ergometrine maleate (p. 2136.2) and is used similarly in the active management of the third stage of labour, and in the prevention and treatment of postpartum or postabortal haemorrhage (p. 2130.2). In the management of the third stage of labour, it may be given in a dose of 200 micrograms intramuscularly after delivery of the anterior shoulder or, at the latest, immediately after delivery of the infant. The same dose may be used for the prevention or treatment of postpartum or postabortal haemorrhage, and may be repeated every 2 to 4 hours as necessary up to a maximum of 5 doses. In emergencies it may be given in similar doses by slow intravenous injection,

over at least 1 minute to reduce the risk of adverse effects, particularly hypertension. During the puerperium, methylergometrine maleate has been given in oral doses of 200 micrograms 3 or 4 times daily for up to a week or 125 to 250 micrograms up to 3 times daily.

Methylergometrine is a metabolite of methysergide (p. 677.1).

Diagnosis and testing. For reference to the use of methylergometrine maleate in the diagnosis of variant angina, see Ergometrine Maleate, p. 2136.3.

Adverse Effects, Treatment, and Precautions

As for Ergometrine Maleate, p. 2136.3 and p. 2137.1.

Overdosage. References.

1. Aeby A, *et al.* Methylergometrine poisoning in children: review of 34 cases. *J Toxicol Clin Toxicol* 2003; 41: 249–53.
2. Bangh SA, *et al.* Neonatal ergot poisoning: a persistent iatrogenic illness. *Am J Perinatol* 2005; 22: 239–43.
3. Ezeweonu-Laryea CC, *et al.* Methylergometrine poisoning in the newborn: report of two cases. *East Afr Med J* 2008; 85: 463–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methylergometrine 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 30/07/11)

Pharmacokinetics

Methylergometrine maleate is reported to be rapidly absorbed when given orally or intramuscularly, with onset of uterine contractions in about 5 to 15 minutes and 2 to 5 minutes, respectively. Oral bioavailability may show considerable interindividual variation. It undergoes extensive first-pass hepatic metabolism and only small amounts of unchanged drug are excreted in the urine. The elimination half-life is reported to be about 2 to 3 hours.

The pharmacokinetics of methylergometrine maleate have been studied after oral doses in healthy subjects[1,2] and in postpartum women.[3] Small amounts of methylergometrine have been detected in breast milk.[4,5]

1. Mäntylä R, *et al.* Methylergometrine (methylergonovine) concentrations in the human plasma and urine. *Int J Clin Pharmacol Biopharm* 1978; 16: 254–7.
2. de Groot ANJA, *et al.* Comparison of the bioavailability and pharmacokinetics of oral methylergometrine in men and women. *Int J Clin Pharmacol Ther* 1995; 33: 328–32.
3. Allonen H, *et al.* Methylergometrine: comparison of plasma concentrations and clinical response of two brands. *Int J Clin Pharmacol Biopharm* 1978; 16: 340–2.
4. Erkkola R, *et al.* Excretion of methylergometrine (methylergonovine) into the human breast milk. *Int J Clin Pharmacol Biopharm* 1978; 16: 579–80.
5. Vogel D, *et al.* Misoprostol versus methylergometrine: pharmacokinetics in human milk. *Am J Obstet Gynecol* 2004; 191: 2168–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Basofortina; *Austria*: Methergin; *Belg.*: Methergin; *Braz.*: Ergometrin; Methergin; *Denm.*: Methergin; *Fin.*: Methergin; *Fr.*: Methergin; *Ger.*: Methergin; *Gr.*: Demergin; Methergin; *Hong Kong*: Ergotyl†; Methergin; *India*: Elmet; Ematrin; Emergin; Ergogin; Ergolin; Ergoriv; G-Metrin; Ingagen-M; Lebergin; Lerin; Mem; Memjet; Mergox; Merzen; Metermin; Methergin; Methging; Methin; Methocin; Methyden; Methygin; Nimeth; Utergin; *Indon.*: Bledstop; Glomethyl; Methergin; Metherinal; Methovin; Metilat; Metvell; Myomergin; Myotonic†; Pospargin; Utergin; *Israel*: Methergin; *Ital.*: Methergin; *Malaysia*: Methergin; *Mex.*: Methergin; *Neth.*: Methergin; *Philipp.*: Comthergin; Ergomed; Josenta; Lerin; Medisyl; Mem; Mergot; Mergotrex; Methergin; Myometril; Obtrin†; Usamema; *Port.*: Methergin; *Rus.*: Methylergobrevin (Метилэргобревин); *Spain*: Methergin; *Swed.*: Methergin; *Switz.*: Methergin; *Thai.*: Ergotyl†; Expogin; Methergin†; Metrine; *Turk.*: Methergin; Metiler; Uterjin; *USA*: Methergine; *Venez.*: Methergin.

Multi-ingredient Preparations. *Philipp.*: Uterine.

Pharmacopoeial Preparations

USP 36: Methylergonovine Maleate Injection; Methylergonovine Maleate Tablets.

Mifepristone (BAN, USAN, rINN)

C-1073; Mifepriston; Mifepristona; Mifépristone; Mifepristoni; Mifepristonum; R-38486; RU-486-6; RU-486; RU-34486; RU-38486; VGX-410C; Мифепристон

11β-(4-Dimethylaminophenyl)-17β-hydroxy-17α-prop-1-ynylestra-4,9-dien-3-one

$C_{29}H_{35}NO_2$ = 429.6

CAS — 84371-65-3

ATC — G03XB01

ATC Vet — QG03XB01

UNII — 320T6RNW1F

Pharmacopoeias. In *Chin.*

Uses and Administration

Mifepristone is a steroid derived from norethisterone that has potent antiprogestogenic activity and sensitises the myometrium to the effects of prostaglandins. It is used in termination of pregnancy (see p. 2139.2), for either medical termination or for softening and dilatation of the cervix before surgical termination of pregnancy. Mifepristone is also used for labour induction after intra-uterine fetal death (see p. 2139.1). Mifepristone also has antiglucocorticoid activity and is used in the treatment of Cushing's syndrome (see below).

In the **medical termination of pregnancy**, the use of mifepristone with a prostaglandin shortens the duration of the procedure and reduces the dose of prostaglandin required. In the UK the licensed regimen for the termination of pregnancies of up to 49 days is a single oral dose of 600 mg of mifepristone followed by a prostaglandin 36 to 48 hours later; prostaglandin treatment may be with either misoprostol 400 micrograms orally or gemeprost 1 mg vaginally. Alternatively, 200 mg of mifepristone may be given as a single oral dose followed, 36 to 48 hours later, by gemeprost 1 mg vaginally. Regimens containing vaginal gemeprost may also be used for the termination of pregnancies of up to 63 days. In the USA the licensed regimen for the termination of pregnancies up to 49 days of gestation is a single oral dose of 600 mg of mifepristone followed 2 days later by 400 micrograms of misoprostol orally, unless abortion has already been completed. As an adjunct to prostaglandin termination of pregnancy beyond the first trimester, the licensed dose in the UK is a single oral dose of mifepristone 600 mg given 36 to 48 hours before scheduled prostaglandin administration.

For **softening and dilatation of the cervix** before surgical termination of pregnancy during the first trimester, a single 200-mg dose of mifepristone orally is given 36 to 48 hours before the procedure.

For labour induction following intra-uterine **fetal death**, oral mifepristone 600 mg is given daily for 2 consecutive days; if labour has not started within 72 hours of the first dose, other methods of induction should be used.

Mifepristone is used to control hyperglycaemia that is secondary to hypercortisolism in endogenous **Cushing's syndrome**; it is given to those patients with secondary type 2 diabetes mellitus or glucose intolerance who are not candidates for surgery or when surgery has failed. The starting dose is 300 mg orally once daily with food. The dose may be increased, according to response, in increments of 300 mg to a maximum of 1.2 g once daily, but to no more than 20 mg/kg daily. The dose should not be increased more frequently than once every 2 to 4 weeks.

When given daily in Cushing's syndrome, a maximum daily dose of 300 mg is recommended when mifepristone must be given with strong inhibitors of the cytochrome P450 isoenzyme CYP3A. Mifepristone may require dose adjustment in patients with hepatic or renal impairment (see below).

Mifepristone has been tried for **other uses** such as postcoital contraception (below), endometriosis (p. 2139.1), uterine fibroids (leiomyomas) (p. 2139.1), and for progestogen-dependent neoplasms such as meningiomas (p. 2139.1). The antiglucocorticoid activity of mifepristone is under investigation in psychotic major depression (below).

General references.

1. Heikinheimo O. Clinical pharmacokinetics of mifepristone. *Clin Pharmacokinet* 1997; 33: 7–17.
2. Mahajan DK, London SN. Mifepristone (RU486): a review. *Fertil Steril* 1997; 68: 967–76.
3. Koide SS. Mifepristone: auxiliary therapeutic use in cancer and related disorders. *J Reprod Med* 1998; 43: 551–60.
4. DeHart RM, Morehead MS. Mifepristone. *Ann Pharmacother* 2001; 35: 707–19.
5. Weingertner A-S, *et al.* Utilisations actuelles et potentielles de la mifépristone en gynécologie-obstétrique et dans les autres disciplines médicales. *J Gynecol Obstet Biol Reprod (Paris)* 2004; 33: 692–702.
6. Tang OS, Ho PC. Clinical applications of mifepristone. *Gynecol Endocrinol* 2006; 22: 655–9.
7. Im A, Appleman LJ. Mifepristone: pharmacology and clinical impact in reproductive medicine, endocrinology and oncology. *Expert Opin Pharmacother* 2010; 11: 481–8.
8. Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. *Contraception* 2010; 82: 442–52.

Administration in hepatic and renal impairment. In patients being treated for Cushing's syndrome, a maximum oral daily dose of 600 mg is recommended for those with mild to moderate hepatic impairment. Studies in patients with severe hepatic impairment are lacking and mifepristone should therefore be avoided in these patients. A maximum daily dose of 600 mg is also recommended for patients with Cushing's syndrome and any degree of renal impairment.

Contraception. Mifepristone has been established as an effective emergency contraceptive (p. 2233.2). Initial studies found an oral 600-mg dose given within 72 hours of coitus to be effective.[1,2] Subsequently lower doses, given up to 120 hours after coitus, have been shown to be well tolerated and as effective as standard emergency contraceptive regimens.[3–5] Studies[3,5,6] and meta-analyses[7,8] have confirmed the efficacy of a 10-mg dose. There was some evidence of a slight dose-response effect; it was calculated that there would be 1 extra pregnancy per 146 women treated if the dose were to be reduced from 25 to 10 mg, but the associated increase in availability of the drug might outweigh this.[8]

The development of a mifepristone-based standard contraceptive (p. 2232.3) has been less successful. Regimens based on daily,[9] weekly,[10,11] or monthly[12,13] doses of mifepristone have been investigated.

1. Glasier A, *et al.* Mifepristone (RU 486) compared with high-dose estrogen and progestogen for emergency postcoital contraception. *N Engl J Med* 1992; 327: 1041–4.
2. Webb AMC, *et al.* Comparison of Yuzpe regimen, danazol, and mifepristone (RU 486) in oral postcoital contraception. *BMJ* 1992; 305: 927–31.
3. von Hertzen H, *et al.* Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002; 360: 1803–10.
4. Ashok PW, *et al.* Mifepristone versus the Yuzpe regimen (PC4) for emergency contraception. *Int J Gynecol Obstet* 2004; 87: 188–93.
5. Hamoda H, *et al.* A randomized trial of mifepristone (10 mg) and levonorgestrel for emergency contraception. *Obstet Gynecol* 2004; 104: 1307–13.
6. Task Force on Postovulatory Methods of Fertility Regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomised trial. *Lancet* 1999; 353: 697–702.
7. Piaggio G, *et al.* Combined estimates of effectiveness of mifepristone 10 mg in emergency contraception. *Contraception* 2003; 68: 439–46.
8. Piaggio G, *et al.* Meta-analyses of randomized trials comparing different doses of mifepristone in emergency contraception. *Contraception* 2003; 68: 447–52.
9. Brown A, *et al.* Daily low-dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double-blind randomized control trial of 2 and 5 mg per day for 120 days. *J Clin Endocrinol Metab* 2002; 87: 63–70.
10. Godfrey EM, *et al.* Low-dose mifepristone for contraception: a weekly versus planned postcoital randomized pilot study. *Contraception* 2004; 70: 41–6.
11. Pei K, *et al.* Weekly contraception with mifepristone. *Contraception* 2007; 75: 40–4.
12. Hapangama DK, *et al.* Feasibility of administering mifepristone as a once a month contraceptive pill. *Hum Reprod* 2001; 16: 1145–50.
13. Narvekar N, *et al.* Toward developing a once-a-month pill: a double-blind, randomized, controlled trial of the effect of three single doses of mifepristone given at midcycle on the pattern of menstrual bleeding. *Fertil Steril* 2006; 86: 819–24.

Cushing's syndrome. Mifepristone has been used to manage the cardiovascular, metabolic, and psychiatric signs and symptoms of Cushing's syndrome (p. 2559.1) because of its antagonist effects at the glucocorticoid receptor.[1–5] Its use has been reported in a small number of patients who have been given mifepristone in [oral] doses ranging from 5 to 30 mg/kg daily.[4] (See Uses and Administration, above, for licensed doses.) The authors of a retrospective study[5] of 20 patients recommended a starting dose of 200 to 400 mg daily, increasing gradually according to response and tolerance to a usual dose of 400 to 800 mg daily. In general the dose may be adjusted every 2 weeks, but increasing the dose by 200 mg every 3 days might be considered for patients needing rapid treatment, such as those with psychosis. They also suggested that a dose above 1 g daily was probably no more effective but associated with more adverse effects. Patients should be monitored for hypokalaemia, which occurs frequently and may require treatment with potassium supplementation and spironolactone. Adrenal insufficiency can also develop, and has been managed by reducing the dose of mifepristone and giving dexamethasone.[5] Others have suggested that long-term mifepristone therapy may increase the risk of endometrial hyperplasia and thyroid dysfunction, and that patients should be monitored accordingly.[4]

1. Nieman LK, *et al.* Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J Clin Endocrinol Metab* 1985; 61: 536–40.
2. van der Lely A-J, *et al.* Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Ann Intern Med* 1991; 114: 143–4.
3. Chu JW, *et al.* Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). *J Clin Endocrinol Metab* 2001; 86: 3568–73.
4. Johanssen S, Allolio B. Mifepristone (RU 486) in Cushing's syndrome. *Eur J Endocrinol* 2007; 157: 561–9.
5. Castinetti F, *et al.* Merits and pitfalls of mifepristone in Cushing's syndrome. *Eur J Endocrinol* 2009; 160: 1003–10.

Depression. Mifepristone is under investigation in the management of depression (p. 398.1) with psychotic features;[1–4] preliminary results suggest some benefit but its efficacy remains to be proven.

1. Belanoff JK, *et al.* An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry* 2002; 52: 386–92.
2. Simpson GM, *et al.* An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *J Clin Psychiatry* 2005; 66: 598–602.
3. Flores BH, *et al.* Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology* 2006; 31: 628–36.

4. DeBattista C, *et al.* Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. *Biol Psychiatry* 2006; 60: 1343–9.

Ectopic pregnancy. Methotrexate with mifepristone may be more effective than methotrexate alone[1,2] for the medical treatment of ectopic pregnancy (p. 823.3), although some have not found the combination to produce any benefit over methotrexate alone in the majority of women.[3]

1. Gazvani MR, *et al.* Mifepristone in combination with methotrexate for the medical treatment of tubal pregnancy: a randomized, controlled trial. *Hum Reprod* 1998; 13: 1987–90.
2. Perdu M, *et al.* Treating ectopic pregnancy with the combination of mifepristone and methotrexate: a phase II nonrandomized study. *Am J Obstet Gynecol* 1998; 179: 640–3.
3. Rozenberg P, *et al.* Medical treatment of ectopic pregnancies: a randomized clinical trial comparing methotrexate-mifepristone and methotrexate-placebo. *Hum Reprod* 2003; 18: 1802–8.

Endometriosis. Some results[1,2] have suggested that mifepristone, which is capable of suppressing ovarian function, may be of benefit in patients with endometriosis (p. 2264.1).

1. Kettel LM, *et al.* Endocrine responses to long-term administration of the antiprogesterone RU486 in patients with pelvic endometriosis. *Fertil Steril* 1991; 56: 402–7.
2. Kettel LM, *et al.* Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU 486). *Am J Obstet Gynecol* 1998; 178: 1151–6.

Fibroids. Mifepristone has been reported to produce significant decreases in uterine and leiomyoma volumes, and to reduce symptoms such as dysmenorrhoea and menorrhagia, when given to patients with fibroids (p. 2281.2). However, data are from small studies using oral doses ranging from 5 to 50 mg daily. Endometrial changes including hyperplasia and cystic glandular dilatation have also been reported in some studies.[1-5]

1. Steinauer J, *et al.* Systematic review of mifepristone for the treatment of uterine leiomyomata. *Obstet Gynecol* 2004; 103: 1331–6.
2. Fiscella K, *et al.* Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. *Obstet Gynecol* 2006; 108: 1381–7.
3. Carbonell Esteve JL, *et al.* Mifepristone for the treatment of uterine leiomyomas: a randomized controlled trial. *Obstet Gynecol* 2008; 112: 1029–36.
4. Bagaria M, *et al.* Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial. *Aust N Z J Obstet Gynaecol* 2009; 49: 77–83.
5. Engman M, *et al.* Mifepristone for treatment of uterine leiomyoma: a prospective randomized placebo controlled trial. *Hum Reprod* 2009; 24: 1870–9.

Labour induction. A few studies[1-3] have reported that mifepristone was effective for cervical ripening and labour induction (p. 2129.1) at term, and sometimes reduced the need for a prostaglandin and oxytocin. However, a dose-finding study[4] found that single oral doses ranging from 50 to 600 mg were no more effective than placebo for inducing labour. The results of a systematic review[7] suggested that mifepristone was better than placebo at ripening the cervix or inducing labour, and might reduce the need for oxytocin. Mifepristone might also reduce the incidence of caesarean section, but increase instrumental delivery. Overall, however, the reviewers concluded that there was insufficient evidence to support its use for labour induction.

Mifepristone is used for cervical ripening and labour induction where intra-uterine fetal death has occurred,[8] usually in oral doses of 600 mg given daily for 2 days. The effective use of a single 200 mg dose, followed by misoprostol given orally and/or vaginally, has also been described.[9,10]

1. Frydman R, *et al.* Labor induction in women at term with mifepristone (RU486): a double-blind, randomized, placebo-controlled study. *Obstet Gynecol* 1992; 80: 972–5.
2. Giacalone PL, *et al.* Cervical ripening with mifepristone before labor induction: a randomized study. *Obstet Gynecol* 1998; 92: 487–92.
3. Elliott CL, *et al.* The effects of mifepristone on cervical ripening and labor induction in primigravidae. *Obstet Gynecol* 1998; 92: 804–9.
4. Stenlund PM, *et al.* Induction of labor with mifepristone—a randomized, double-blind study versus placebo. *Acta Obstet Gynecol Scand* 1999; 78: 793–8.
5. Wing DA, *et al.* Mifepristone for preinduction cervical ripening beyond 41 weeks' gestation: a randomized controlled trial. *Obstet Gynecol* 2000; 96: 543–8.
6. Berkane N, *et al.* Use of mifepristone to ripen the cervix and induce labor in term pregnancies. *Am J Obstet Gynecol* 2005; 192: 114–20.
7. Hapangama D, Neilson JP. Mifepristone for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 10/09/09).
8. Cabrol D, *et al.* Induction of labor with mifepristone (RU 486) in intrauterine fetal death. *Am J Obstet Gynecol* 1990; 163: 540–2.
9. Wagaarachchi PT, *et al.* Medical management of late intrauterine death using a combination of mifepristone and misoprostol. *BJOG* 2002; 109: 443–7.
10. Väyrynen W, *et al.* Misoprostol-only versus mifepristone plus misoprostol in induction of labor following intrauterine fetal death. *Acta Obstet Gynecol Scand* 2007; 86: 701–5.

Meningioma. Mifepristone has been used successfully in some patients with inoperable meningioma,[1-4] a brain tumour that may be progestogen-receptor positive. It has been given long term in oral doses of 200 mg daily, in some cases for more than 10 years. Adverse effects from long-term therapy have included fatigue, hot flushes, nausea, and depression; gynaecomastia has occurred in men and breast tenderness in women. Cessation of menstruation during mifepristone therapy occurs in premenopausal women, and there have been isolated cases of endometrial hyperplasia in pre- and postmenopausal women.

1. Grunberg SM, *et al.* Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. *J Neurosurg* 1991; 74: 861–6.
2. Lamberts SWJ, *et al.* Mifepristone (RU 486) treatment of meningiomas. *J Neurol Neurosurg Psychiatry* 1992; 55: 486–90.
3. Spitz IM, *et al.* Management of patients receiving long-term treatment with mifepristone. *Fertil Steril* 2005; 84: 1719–26.
4. Grunberg SM, *et al.* Long-term administration of mifepristone (RU486): clinical tolerance during extended treatment of meningioma. *Cancer Invest* 2006; 24: 727–33.

Termination of pregnancy. Mifepristone sensitises the myometrium to prostaglandins, increases uterine contractility, and softens and dilates the cervix.[1] It is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with prostaglandins for the termination of pregnancy (p. 2131.3). Mifepristone has also been tried with methotrexate in the treatment of ectopic pregnancy (see above) and may be used to induce labour where intra-uterine fetal death has occurred (see above).

Mifepristone, followed 36 to 48 hours later by a prostaglandin, is an effective medical alternative to surgical methods for the termination of pregnancy in the *first trimester*.[1] Efficacy decreases with increasing gestational age, and the success rate may be affected by the choice of prostaglandin, its dose, and route of administration. Termination success rates are highest for gestations of up to 49 days; after this the success rate for mifepristone with oral misoprostol tends to decrease compared with other regimens.[2] Vaginal gemeprost may be used with mifepristone for gestations of up to 63 days.[1] The usual dose of oral mifepristone is 600 mg, although lower doses of 200 and 400 mg have been studied in various regimens with prostaglandins and found to be as effective.[1,3] A similar efficacy was also shown in a comparison of 100 and 200 mg doses.[4] However, a further reduction to 50 mg significantly reduced efficacy.[1,3]

Although surgical termination is commonly used for pregnancies of 9 to 13 weeks, there is increasing evidence to support the use of medical termination using mifepristone followed by misoprostol. A regimen using oral mifepristone 200 mg, followed 36 to 48 hours later by misoprostol 800 micrograms vaginally, has been described.[5,6] Two further vaginal doses of misoprostol 400 micrograms were given at intervals of 3 hours if the products of conception had not been passed (these doses could be given orally if vaginal bleeding was beavier than a normal period[4]). Surgical evacuation was then used if necessary. In a large case series of 1076 women,[7] medical abortion was successful in 95.8%. A regimen of oral mifepristone 200 mg, followed 36 to 48 hours later by misoprostol 800 micrograms vaginally (or 600 micrograms sublingually), was used, with up to 5 further doses of misoprostol 400 micrograms (vaginally or sublingually) given at intervals of 3 hours if needed. The mean number of misoprostol doses used was 2.31.

Mifepristone is also used to ripen the cervix before vacuum aspiration for surgical termination in the first trimester. Oral doses of 600 mg have been used, but lower doses were also found to be more effective than placebo[8,9] and as effective as prostaglandins;[10-12] consequently, a dose of 200 mg is now often used.

Mifepristone followed by a prostaglandin may also be used for medical termination in the *second trimester* (mid-trimester termination; gestation of 13 to 24 weeks).[13,14] Similarly to early termination, a study found mifepristone 200 mg orally to be as effective as 600 mg when followed by misoprostol.[15] Further retrospective reviews have also reported mifepristone 200 mg followed by misoprostol[16] or gemeprost[17] to be effective.

In the UK the Royal College of Obstetricians and Gynaecologists' guidelines[18] for both early and mid-trimester terminations include the following regimens:

- for gestation up to 63 days (9 weeks), mifepristone 200 mg orally followed 24 to 72 hours later by misoprostol 800 micrograms vaginally; if abortion has not occurred 4 hours after administration of misoprostol in women at 49 to 63 days of gestation, a further dose of misoprostol 400 micrograms may be given orally or vaginally
- for gestation between 9 and 13 weeks, mifepristone 200 mg orally followed 36 to 48 hours later by misoprostol 800 micrograms vaginally; a maximum of 4 further doses of misoprostol 400 micrograms may be given every 3 hours, orally or vaginally, if necessary
- for mid-trimester termination (13 to 24 weeks), mifepristone 200 mg orally followed 36 to 48 hours later by misoprostol 800 micrograms vaginally, then up to 4 further doses of misoprostol 400 micrograms given every 3 hours orally

Mifepristone followed by a prostaglandin has also been used in early pregnancy loss, particularly missed miscarriage, and has been reported to be an effective alternative to surgical evacuation.[19,20] As for termination, mifepristone doses of 200 and 600 mg orally, followed by misoprostol, appear to be equally effective,[21] although some studies[22,23] suggest that pretreatment with mifepristone does not improve the expulsion rate compared with vaginal or oral misoprostol alone.

1. Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with a prostaglandin analogue. *Contraception* 2006; 74: 66–86.
2. Kahn JG, *et al.* The efficacy of medical abortion: a meta analysis. *Contraception* 2000; 61: 29–40.
3. Marions L. Mifepristone dose in the regimen with misoprostol for medical abortion. *Contraception* 2006; 74: 21–5.
4. von Hertzen H, *et al.* WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomised factorial controlled equivalence trial. *BJOG* 2009; 116: 381–9.
5. Ashok PW, *et al.* Termination of pregnancy at 9-13 weeks' amenorrhoea with mifepristone and misoprostol. *Lancet* 1998; 352: 542–3.
6. Ashok PW, *et al.* A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation. *Hum Reprod* 2002; 17: 92–8.
7. Hamoda H, *et al.* Medical abortion at 9–13 weeks' gestation: a review of 1076 consecutive cases. *Contraception* 2005; 71: 327–32.
8. WHO. The use of mifepristone (RU 486) for cervical preparation in first trimester pregnancy termination by vacuum aspiration. *Br J Obstet Gynaecol* 1990; 97: 260–6.
9. WHO Task Force on Postovulatory Methods of Fertility Regulation. Cervical ripening with mifepristone (RU 486) in late first trimester abortion. *Contraception* 1994; 50: 461–75.
10. Henshaw RC, Templeton AA. Pre-operative cervical preparation before first trimester vacuum aspiration: a randomized controlled comparison between gemeprost and mifepristone (RU 486). *Br J Obstet Gynaecol* 1991; 98: 1025–30.
11. Ngai SW, *et al.* Oral misoprostol versus mifepristone for cervical dilatation before vacuum aspiration in first trimester nulliparous pregnancy: a double blind prospective randomised study. *Br J Obstet Gynaecol* 1996; 103: 1120–3.
12. Ashok PW, *et al.* Mifepristone versus vaginally administered misoprostol for cervical priming before first-trimester termination of pregnancy: a randomized, controlled study. *Am J Obstet Gynecol* 2000; 183: 998–1002.
13. Rodger M, Baird D. Pretreatment with mifepristone (RU486) reduces interval between prostaglandin administration and expulsion in second trimester abortion. *Br J Obstet Gynaecol* 1990; 97: 41–5.
14. Thong KJ, Baird DT. Induction of second trimester abortion with mifepristone and gemeprost. *Br J Obstet Gynaecol* 1993; 100: 758–61.
15. Webster D, *et al.* A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. *Br J Obstet Gynaecol* 1996; 103: 706–9.
16. Ashok PW, *et al.* Midtrimester medical termination of pregnancy: a review of 1002 consecutive cases. *Contraception* 2004; 69: 51–8.
17. Tang OS, *et al.* Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases. *Contraception* 2001; 64: 29–32.
18. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7 (issued September 2004). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/NEBInducedAbortionfull.pdf (accessed 22/08/10)
19. Chia KV, Ogbo VI. Medical termination of missed abortion. *J Obstet Gynaecol* 2002; 22: 184–6.
20. Minimalldi M, *et al.* A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. *Fertil Steril* 2006; 86: 367–72.
21. Coughlin LB, *et al.* Medical management of first trimester miscarriage (blighted ovum and missed abortion): is it effective? *J Obstet Gynaecol* 2004; 24: 69–71.
22. Graulund A, *et al.* Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation: a multi-center trial in Copenhagen county, Denmark. *Acta Obstet Gynecol Scand* 2002; 81: 1060–5.
23. Stockheim D, *et al.* A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. *Fertil Steril* 2006; 86: 956–60.

Adverse Effects and Treatment

Uterine bleeding and cramps often occur after the use of mifepristone in procedures for the termination of pregnancy, and will occur in almost all patients after the addition of a prostaglandin. Bleeding typically continues for about 9 to 16 days, and may be severe enough to warrant curettage and transfusion in a small proportion of patients. However, prolonged heavy bleeding may also be a sign of incomplete abortion or other complications that require medical or surgical intervention. Other adverse effects of mifepristone include malaise, dizziness, chills, fever, headache, diarrhoea, nausea, vomiting, rashes, and urticaria; although some of these effects may be caused by the prostaglandin given after mifepristone.

Serious, sometimes fatal, infections have occurred in women undergoing abortion, although no causal relationship has been established between these events and the use of mifepristone.

When given in the management of Cushing's syndrome, the most frequent adverse effects of mifepristone are gastrointestinal disturbances, decreased appetite, fatigue, drowsiness, dizziness, headache, anxiety, dyspnoea, peripheral oedema, and hypertension. Arthralgia, myalgia, and back pain can also occur. Hypokalaemia is a common adverse effect, and serum-potassium should be measured before and 1 to 2 weeks after starting mifepristone, during any dose adjustment, and periodically throughout therapy. A mineralocorticoid antagonist, such as spironolactone, may be needed if potassium supplementation does not

control hypokalaemia. Abnormal thyroid function tests have been reported. Endometrial thickening, cystic dilatation of endometrial glands, and vaginal bleeding have been found in women treated with continuous mifepristone. Mifepristone prolongs the QTc interval in a dose-dependent way.

Symptoms of adrenal insufficiency may develop in patients being treated with mifepristone for Cushing's syndrome. However, serum-cortisol concentrations stay raised during mifepristone therapy and do not provide an accurate assessment of hypoadrenalism. In such cases, mifepristone should be stopped and glucocorticoid therapy given; high doses may be needed to overcome the receptor blockade of mifepristone. Treatment may be restarted at a lower mifepristone dose after symptoms resolve.

Effects on the cardiovascular system. For a report of a woman who died from cardiovascular shock during an abortion induced by mifepristone followed by sulprostone, see p. 2145.3.

Effects on the fetus. Studies in *rabbits*, but not *rats* or *mice*, suggest mifepristone causes fetal malformation. There have been reports of normal fetal development after the use of a single dose of mifepristone alone in mothers who subsequently decided to continue their pregnancy.[1,2] However, in two reports, use of mifepristone was possibly related to malformations of the fetus including sirenomelia.[2,3] Cerebellar agenesis has been reported after a failed medical termination using mifepristone and gemeprost (see under Dinoprostone, p. 2135.2).

1. Lim BH, *et al.* Normal development after exposure to mifepristone in early pregnancy. *Lancet* 1990; 336: 257–8.
2. Pons J-C, *et al.* Development after exposure to mifepristone in early pregnancy. *Lancet* 1991; 338: 763.
3. Sitruk-Ware R, *et al.* Fetal malformation and failed medical termination of pregnancy. *Lancet* 1998; 352: 323.

Infection. Patients with endogenous Cushing's syndrome are at risk of opportunistic infection. The development of *Pneumocystis jirovecii* pneumonia shortly after starting mifepristone has been described. The authors suggested that the antiglucocorticoid effect of mifepristone could allow a restoration of the immune response to pre-existing subclinical *P. jirovecii* infection, resulting in the precipitation of clinical symptoms of pneumonia.[1]

1. Oosterhuis JK, *et al.* Life-threatening Pneumocystis jiroveci pneumonia following treatment of severe Cushing's syndrome. *Neth J Med* 2007; 65: 215–17.

TOXIC SHOCK SYNDROME. Fatal toxic shock syndrome occurred in 5 women who underwent medical termination of pregnancy using mifepristone and misoprostol.[1,2] In 4 cases it was specified that mifepristone 200 mg had been given orally, followed by misoprostol 800 micrograms vaginally.[2] Within a week of termination, these patients presented with signs and symptoms that included abdominal pain, nausea and vomiting, tachycardia, hypotension, oedema, haemoconcentration, profound leucocytosis, and absence of fever. Postmortem examination found evidence of endometritis and toxic shock syndrome that was attributed to *Clostridium sordellii* infection. This is an infrequent human pathogen, but the authors of one report[2] noted that *C. sordellii* infection of the genital tract had also been reported in 8 women after delivery, suggesting that pregnancy, childbirth, or termination of pregnancy may predispose a small number of women to acquire this organism, and that associated dilatation of the cervix may allow for ascending infection.

Although there has also been some speculation about the possible mechanisms, both pharmacological[3] and physical,[4] by which oral mifepristone or vaginal misoprostol might potentiate *C. sordellii* infection, a causal relationship between these drugs and the 5 reported deaths has not been established.[5] A review[6] of further cases found that infection can also occur after miscarriage, that it can occur with regimens other than oral mifepristone followed by vaginal misoprostol, and that *C. perfringens* infection may also cause toxic shock after termination. A retrospective analysis[7] of data from 227 823 women who underwent medical termination of pregnancy found a significant reduction in the rate of serious infection after the route of misoprostol delivery was changed from vaginal to buccal. However, the relative effect of this change was difficult to estimate because routine infection reduction measures (screening for sexually transmitted infection or prophylactic doxycycline) had been introduced at the same time.

1. Sinave C, *et al.* Toxic shock syndrome due to Clostridium sordellii: a dramatic postpartum and postabortion disease. *Clin Infect Dis* 2002; 35: 1441–3.
2. Fischer M, *et al.* Fatal toxic shock syndrome associated with Clostridium sordellii after medical abortion. *N Engl J Med* 2005; 353: 2352–60.
3. Miech RP. Pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii. *Ann Pharmacother* 2005; 39: 1483–8.
4. Sicard D, Chauvelot-Moachon L. Comment: pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii. *Ann Pharmacother* 2005; 39: 2142–3.
5. FDA. Questions and answers on Mifeprex (mifepristone) (issued 4th November, 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111341.htm (accessed 29/03/11)
6. Cohen AL, *et al.* Toxic shock associated with Clostridium sordellii and Clostridium perfringens after medical and spontaneous abortion. *Obstet Gynecol* 2007; 110: 1027–33.
7. Fjerstad M, *et al.* Rates of serious infection after changes in regimens for medical abortion. *N Engl J Med* 2009; 361: 145–51.

Precautions

The use of mifepristone for termination of pregnancy is contra-indicated in women with a confirmed or suspected ectopic pregnancy, because medical termination using mifepristone and a prostaglandin will not be effective (for use with methotrexate, see p. 2139.1). The expected symptoms of a medical termination may also be similar to those of a ruptured ectopic pregnancy. In women being treated for Cushing's syndrome, pregnancy must be excluded before starting mifepristone or if treatment is interrupted for more than 14 days, and non-hormonal contraception should be used during treatment and for 1 month after stopping mifepristone. Women who develop abnormal vaginal bleeding should be investigated for endometrial changes. Mifepristone should be given with care to patients with haemostatic disorders or anaemia.

During treatment for Cushing's syndrome, patients with heart failure or cardiovascular disease should be monitored because raised serum-cortisol concentrations, which may activate mineralocorticoid receptors, are not reduced by mifepristone.

Mifepristone is contra-indicated in patients with chronic adrenal failure. It should be avoided in patients with serious conditions being treated with systemic corticosteroids, such as immunosuppression after transplantation. Mifepristone should be given with care in other chronic conditions requiring corticosteroid therapy, including inhaled therapy in asthma; it should be avoided in severe uncontrolled asthma. Mifepristone should be used with caution in hepatic or renal impairment, and is not recommended for termination of pregnancy in women with renal or hepatic failure.

Breast feeding. Mifepristone was detected in the breast milk of 10 lactating women who underwent medical termination of pregnancy using mifepristone (600 mg orally) and misoprostol. Concentrations of mifepristone were found to be the highest in the first 12 hours after the dose, and then declined over the next 7 days. However, the measured concentrations were low and the authors estimated that an exclusively breast-fed infant aged 6 to 12 months might ingest a relative dose of up to 1.5% of that given to the mother. Mifepristone was below the detection limit in 2 other women given a 200-mg dose of mifepristone. It was suggested that breast feeding could continue during medical termination using mifepristone, especially if a dose of 200 mg was used.[1] Licensed product information advises against breast feeding by women given mifepristone.

1. Sääv I, *et al.* Medical abortion in lactating women—low levels of mifepristone in breast milk. *Acta Obstet Gynecol Scand* 2010; 89: 618–22.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mifepristone 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 30/07/11)

Interactions

The metabolism of mifepristone is mediated by the cytochrome P450 isoenzyme CYP3A4. Theoretically, use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of mifepristone. The impact of this on the efficacy of mifepristone for the termination of pregnancy is unknown. During treatment for Cushing's syndrome, mifepristone and strong inhibitors of CYP3A4 should only be used together with extreme caution and the dose of mifepristone limited (see Uses and Administration, p. 2138.2); moderate inhibitors may be used with caution. The use of mifepristone with CYP3A4 inducers should be avoided.

Mifepristone is an inhibitor of CYP3A4. Continuous concomitant use is contra-indicated with simvastatin and lovastatin, and with CYP3A4 substrates that have a narrow therapeutic index. Other substrates should be used with caution. Mifepristone is also an inhibitor of CYP2C8, CYP2C9, and CYP2B6, and could increase the exposure to drugs metabolised by these enzymes.

Mifepristone should be used with caution in women also receiving anticoagulant therapy. Through its antagonist effects, mifepristone reduces the efficacy of corticosteroids and hormonal contraceptives.

NSAIDs. The effects of mifepristone on the uterus and cervix may be mediated by increased prostanoid synthesis resulting from its inhibitory effect on progesterone. It has been suggested that *aspirin* and *NSAIDs*, which are prostaglandin synthetase inhibitors, might alter the efficacy of mifepristone. However, a placebo-controlled study[1] in 28 women found that in the 13 given *naproxen* 500 mg orally 60, 48, 36, 24, and 12 hours before surgical termination of pregnancy the efficacy of mifepristone 100 mg given orally to soften the cervix was not reduced. Also, NSAIDs did not affect medical termination using mifepristone followed by misoprostol (see p. 2142.3).

1. Rådestad A, Bygdeman M. Cervical softening with mifepristone (RU 486) after pretreatment with naproxen: a double-blind randomized study. *Contraception* 1992; 45: 221–7.

Pharmacokinetics

Peak plasma concentrations of mifepristone occur about 1 to 2 hours after a single oral dose, and between 1 and 4 hours after multiple doses; bioavailability is about 70%. Mifepristone is about 98% bound to plasma proteins, mainly α_1-acid glycoprotein. Elimination is biphasic; a slow phase is followed by a more rapid terminal phase, with an elimination half-life of about 18 hours. At steady state, the half-life is about 85 hours. Mifepristone undergoes hepatic oxidative metabolism, mainly by the cytochrome P450 isoenzyme CYP3A4, and metabolites are excreted in the bile and eliminated in the faeces. Only a small fraction is detected in the urine. Mifepristone is distributed into breast milk.

Reviews.

1. Sarkar NN. Mifepristone: bioavailability, pharmacokinetics and use-effectiveness. *Eur J Obstet Gynecol Reprod Biol* 2002; 101: 113–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Mifegyne; *Belg.*: Mifegyne; *China*: Bi Yun (碧韵); Han Zhu Ting (含珠停); Hou Ding Nuo (后定诺); Mi Fu (米福); Mifolian (弗乃尔); Nuo Lv Ting (诺虑婷); Si Mi An (司米安); Xiyin (息隐); *Denm.*: Mifegyne; *Fin.*: Mifegyne; *Fr.*: Mifegyne; *Ger.*: Mifegyne; *Gr.*: Mifegyne; *India*: Abo Pill; Abortom; Cedate; Elmif; Mefipil; MF-Kare; Mifebort; Mifegest; Mifeprin; Miferiv; Mistone; MT Pill; *Israel*: Mifegyne; *Neth.*: Mifegyne; *Norw.*: Mifegyne; *NZ*: Mifegyne; *Port.*: Mifegyne; *Rus.*: Gynepriston (Гинепристон); Gynestril (Гинестрил); Mifegyn (Мифегин); Mifeprex (Мифепрекс); Mifolian (Мифолиан); Pencroftonum (Пенкрофтон); *S.Afr.*: Mifegyne; *Spain*: Mifegyne; *Swed.*: Mifegyne; *Switz.*: Mifegyne; *UK*: Mifegyne; *Ukr.*: Ginepriston (Гинепристон); Miropristor (Миропристон); *USA*: Korlym; Mifeprex.

Multi-ingredient Preparations. *China*: Zi Yun (紫韵); *Neth.* Medabon.

Misoprostol *(BAN, USAN, rINN)*

Misoprostolii; Misoprostolo; Misoprostolum; Mizoprostol; SC-29333; Мизопростол.

(±)-Methyl 7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate; (±)-Methyl (13*E*)-11,16-dihydroxy-16-methyl-9-oxoprost-13-enoate.

$C_{22}H_{38}O_5$=382.5

CAS — 59122-46-2.

ATC — A02BB01; G02AD06.

ATC Ver — QA02BB01; QG02AD06.

UNII — 0E43V0BB57.

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

Ph. Eur. 8: (Misoprostol). A clear, colourless or yellowish hygroscopic, oily liquid. Practically insoluble in water soluble in alcohol; sparingly soluble in acetonitrile. Store in airtight containers at -20 degrees.

USP 36: (Misoprostol). A clear, colourless or light yellow viscous liquid. Very slightly soluble in water. Store in airtight containers at a temperature of -10 degrees to -2 degrees.

Uses and Administration

Misoprostol is a synthetic analogue of alprostadil (prostaglandin E_1; p. 2352.2).

It is used in the treatment of benign gastric and duodenal **ulceration** (p. 2141.2) including that associated with NSAIDs. The usual oral dose is 800 micrograms daily in two to four divided doses, taken with food and at bedtime. Treatment is initially given for at least 4 weeks, even if symptoms are relieved sooner, and may continue for up to 8 weeks if necessary. Further courses may be used to treat relapse.

Misoprostol is also used prophylactically with NSAIDs to prevent NSAID-induced ulcers. The usual oral dose is 200 micrograms two to four times daily. A dose of 100 micrograms four times daily may be used in patients not tolerating the higher dose. Some preparations of

NSAIDs contain misoprostol in an attempt to limit their adverse effects on the gastrointestinal mucosa.

Misoprostol may be used to ripen the cervix before surgical **termination of pregnancy** (below) in the first trimester. A single oral dose of misoprostol 400 micrograms is given 3 to 4 hours before surgery. It may also be used for medical termination of pregnancy at up to 49 days of amenorrhoea, in a single oral dose of 400 micrograms given 36 to 48 hours after mifepristone. Misoprostol has also been used for induction of labour (see below) and in the management of postpartum haemorrhage (see below).

General reviews.

1. Goldberg AB, *et al.* Misoprostol and pregnancy. *N Engl J Med* 2000; 344: 38–47.
2. Blanchard K, *et al.* Misoprostol for women's health: a review. *Obstet Gynecol* 2002; 99: 316–32.
3. Lokugamage AU, *et al.* Misoprostol and pregnancy: ever-increasing indications of effective usage. *Curr Opin Obstet Gynecol* 2003; 15: 513–18.
4. Chong YS, *et al.* Misoprostol: a quarter century of use, abuse, and creative misuse. *Obstet Gynecol Surv* 2004; 59: 128–40.
5. Weeks A, Faúndes A. Misoprostol in obstetrics and gynecology. *Int J Gynaecol Obstet* 2007; 99 suppl: S156–S159.
6. Elati A, Weeks AD. The use of misoprostol in obstetrics and gynaecology. *BJOG* 2009; 116 (suppl 1): 61–9.
7. Chokrachat C. Clinical use of misoprostol in nonpregnant women: review article. *J Minim Invasive Gynecol* 2010; 17: 449–55.

Labour induction and augmentation. Prostaglandins are well established for the induction of labour (p. 2129.1) at term and misoprostol has been widely investigated for this indication. A systematic review[1] of studies of misoprostol given *vaginally* found that it increased cervical ripening and induced labour. It was more effective than vaginal or intracervical dinoprostone, reducing the need for oxytocin augmentation and improving the rate of vaginal delivery achieved within 24 hours. It was also found to be more effective than intravenous oxytocin. Most studies used misoprostol tablets in a dose of 50 micrograms vaginally every 4 hours, but reported doses have varied from 25 micrograms every 2 to 3 hours, to 100 micrograms every 6 to 12 hours. Low doses of misoprostol resulted in more use of oxytocin, but caused less uterine hyperstimulation. Although unlicensed, misoprostol is reported to be used outside clinical studies particularly in the USA, and the American College of Obstetricians and Gynecologists has recommended a dose of 25 micrograms intravaginally every 3 to 6 hours.[2]

Misoprostol has also been given *orally* but this route is less well established. Reported doses have varied widely but most studies have used 50 micrograms every 4 hours. Some reviews have found oral to be less effective than vaginal misoprostol.[2,3] However, others[4] have concluded that oral use produces similar outcomes to vaginal misoprostol, but that comparison is complicated by the wide variation in doses. Overall, oral misoprostol appears to be at least as effective as vaginal dinoprostone, but because of limited data it should be used with caution.[4] The risk of uterine hyperstimulation may be increased with misoprostol by either route, particularly when given vaginally[4] or at higher doses,[1,4] and it should not be used in women with scarred uteri from previous caesarean delivery or uterine surgery[2] (see also Effects on the Uterus, under Adverse Effects of Dinoprostone, p. 2135.2). There has also been some limited investigation of misoprostol given *sublingually*.[3,5,6]

Misoprostol has been used for labour induction for terminations in the second and third trimesters for fetal anomaly or after **intra-uterine fetal death**. Vaginal misoprostol appears to be as effective as other prostaglandins, and more effective than oral use. Studied dosage regimens have varied considerably, including cumulative doses ranging from 400 to 3200 micrograms over 24 hours, and dosage intervals of 3 to 12 hours.[7] Misoprostol has also been used with mifepristone for intra-uterine fetal death (see Labour Induction, p. 2139.1).

Misoprostol may also be used for active management of the third stage of labour (see Postpartum Haemorrhage, below).

1. Hofmeyr GJ, *et al.* Vaginal misoprostol for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 09/02/11).
2. Wing DA. A benefit-risk assessment of misoprostol for cervical ripening and labour induction. *Drug Safety* 2002; 25: 665–76.
3. Bartusevicius A, *et al.* Oral, vaginal and sublingual misoprostol for induction of labor. *Int J Gynecol Obstet* 2005; 91: 2–9.
4. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
5. Shetty A, *et al.* Sublingual misoprostol for the induction of labor at term. *Am J Obstet Gynecol* 2002; 186: 72–6.
6. Shetty A, *et al.* Sublingual compared with oral misoprostol in term labour induction: a randomised controlled trial. *Br J Obstet Gynaecol* 2002; 109: 645–50.
7. Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 09/02/11).

Organ and tissue transplantation. Misoprostol 200 micrograms orally four times daily improved renal function in ciclosporin-treated recipients of renal transplants.[1] The number of patients who had acute graft rejection was lower in the misoprostol group than in the placebo group. However, another study[2] did not indicate any difference in the incidence of rejection episodes or in renal function when misoprostol was added to immunosuppressant regimens for kidney transplantation, and misoprostol does not appear to have gained a role in the usual management of renal transplantation (p. 1935.2).

1. Moran M, *et al.* Prevention of acute graft rejection by the prostaglandin E_1 analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. *N Engl J Med* 1990; 322: 1183–8.
2. Pouteil-Noble C, *et al.* Misoprostol in renal transplant recipients: a prospective, randomized, controlled study on the prevention of acute rejection episodes and cyclosporin A nephrotoxicity. *Nephrol Dial Transplant* 1994; 9: 552–5.

Peptic ulcer disease. Misoprostol is used in the prophylaxis and treatment of peptic ulceration (p. 1813.2) in patients taking NSAIDs. There is good evidence that misoprostol can reduce the risk of gastric and duodenal ulcer formation in patients on long-term NSAID treatment,[1–4] and it appears more effective in this respect than histamine H_2-antagonists,[1] for which evidence of benefit against gastric injury is less persuasive. However, misoprostol's abdominal adverse effects, particularly diarrhoea and abdominal cramps, may limit its usefulness and patient acceptability. Omeprazole, which is equally effective in preventing NSAID-induced ulceration, is better tolerated.[3] Improved formulations, in which the active isomer of misoprostol is bound to a polymer, may reduce adverse effects.[5]

1. Koch M, *et al.* Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury: a meta-analysis of randomized controlled clinical trials. *Arch Intern Med* 1996; 156: 2321–32.
2. Champion GD, *et al.* NSAID-induced gastrointestinal damage: epidemiology, risk and prevention, with an evaluation of the role of misoprostol: an Asia-Pacific perspective and consensus. *Drugs* 1997; 53: 6–19.
3. Hawkey CJ, *et al.* Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. *N Engl J Med* 1998; 338: 727–34.
4. Rostom A, *et al.* Prevention of NSAID-induced gastroduodenal ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 30/06/08).
5. Chen D, *et al.* Stabilization and sustained-release effect of misoprostol with methacrylate copolymer. *Int J Pharmaceutics* 2000; 203: 141–8.

Postpartum haemorrhage. Prostaglandins, usually given parenterally, have an accepted role in the management of established *postpartum haemorrhage* (p. 2130.2) not controlled by oxytocin and ergot preparations. There have been reports[1–3] of the successful use of rectal misoprostol to control postpartum haemorrhage, using single doses of 800 or 1000 micrograms. A review[4] found that there was some evidence for reduced blood loss with lower doses of misoprostol, and suggested that oral, sublingual, rectal, or a combination of these, might be the most effective routes; possible regimens were 200 to 400 micrograms sublingually or rectally, or similar doses plus 200 micrograms orally. It also suggested that the oral dose of misoprostol should not exceed 600 micrograms because of the risk of hyperpyrexia. WHO has suggested that in settings where other uterotonics are not available or if all other measures fail, misoprostol may be used as a last resort in a dose of 200 to 800 micrograms orally or sublingually.[5] Subsequently, a large study provided evidence of sublingual misoprostol 800 micrograms being less effective than intravenous oxytocin for control of postpartum bleeding in women who had not received prophylactic oxytocin during labour.[6] In women who had already received prophylactic oxytocin, studies have provided variable results: one study found that sublingual misoprostol 600 micrograms was no better than placebo for treatment,[7] while another found misoprostol 800 micrograms to be clinically equivalent to oxytocin.[8] All 3 studies noted the increased incidence of shivering and fever associated with misoprostol. There have also been a few cases in which intra-uterine misoprostol 800 micrograms has controlled refractory secondary postpartum haemorrhage.[9,10]

Misoprostol has also been given immediately after delivery in the *active management of third-stage labour*. In a study[11] of more than 18 500 women treated in hospital, which compared oral misoprostol 600 micrograms with intramuscular or intravenous oxytocin, a higher proportion of women who received misoprostol had blood loss of at least 1000 mL and required additional oxytocics. Misoprostol was also associated with significantly more shivering and pyrexia. The results of this large study suggest that parenteral oxytocin is preferred for active management, but it has been argued that misoprostol may be particularly useful in preventing postpartum haemorrhage in developing countries where there is limited access to healthcare facilities and parenteral oxytocics.[12–14] Two placebo-controlled studies have addressed this argument, reporting that oral[15] or sublingual[16] misoprostol used in rural primary healthcare settings reduced postpartum haemorrhage, particularly severe haemorrhage (1000 mL or more). A systematic review[17] concluded that oral misoprostol was less effective than injectable oxytocics in reducing blood loss and the use of additional oxytocics, but that it may be used where no injectable uterotonic is available. WHO has recommended that in the absence of personnel trained to offer active management of the third stage of labour, a trained health worker should offer misoprostol 600 micrograms orally immediately after the birth of the baby, without active intervention to deliver the placenta.[5]

1. O'Brien P, *et al.* Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. *Obstet Gynecol* 1998; 92: 212–4.
2. Lokugamage AU, *et al.* A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstet Gynecol Scand* 2001; 80: 835–9.
3. Shojai R, *et al.* Le misoprostol par voie rectale dans l'hémorragie de la délivrance: rectal misoprostol for postpartum hemorrhage. *Gynecol Obstet Fertil* 2004; 32: 703–7.
4. Hofmeyr GJ, *et al.* Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG* 2005; 112: 547–53.
5. WHO, Department of Reproductive Health and Research. WHO statement regarding the use of misoprostol for postpartum haemorrhage prevention and treatment (issued 2009). Available at: http://whqlibdoc.who.int/hq/2009/WHO_RHR_09.22_eng.pdf (accessed 18/09/09)
6. Winikoff B, *et al.* Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. *Lancet* 2010; 375: 210–16.
7. Widmer M, *et al.* Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. *Lancet* 2010; 375: 1808–13.
8. Blum J, *et al.* Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet* 2010; 375: 217–23.
9. Adekanmi OA, *et al.* Intrauterine misoprostol for the treatment of severe recurrent atonic secondary postpartum haemorrhage. *BJOG* 2001; 108: 541–2.
10. Oboro VO, *et al.* Intrauterine misoprostol for refractory postpartum hemorrhage. *Int J Gynecol Obstet* 2003; 80: 67–8.
11. Gülmezoglu AM, *et al.* WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet* 2001; 358: 689–95.
12. Darney PD. Misoprostol: a boon to safe motherhood...or not? *Lancet* 2001; 358: 682–3.
13. Shannon C, Winikoff B. Use of misoprostol in third stage of labour. *Lancet* 2002; 359: 709.
14. Langenbach C. Misoprostol in preventing postpartum hemorrhage: a meta-analysis. *Int J Gynecol Obstet* 2006; 92: 10–18.
15. Derman RJ, *et al.* Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. *Lancet* 2006; 368: 1248–53.
16. Høj L, *et al.* Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial. Abridged version: *BMJ* 2005; 331: 723–7. Full version: http://www.bmj.com/cgi/content/full/331/7519/723 (accessed 30/06/08)
17. Gülmezoglu AM, *et al.* Prostaglandins for preventing postpartum haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).

Termination of pregnancy. Prostaglandins are widely used for the termination of pregnancy (p. 2131.3) and misoprostol has been studied both for cervical preparation and for inducing uterine contractions.

In the *first trimester*, misoprostol is used for cervical ripening before surgical termination; it has been reported to be effective when given orally, sublingually, or vaginally,[1–4] usually in a dose of 400 micrograms. Oral misoprostol (400 micrograms) given after mifepristone is effective in medical termination of early pregnancy of up to 63 days, and especially so at up to 49 days.[5,6] Misoprostol 800 micrograms has also been given vaginally after mifepristone,[7–10] and a regimen of 2 or 3 doses of sublingual misoprostol after oral mifepristone has been reported to be effective.[11] When given as a single dose of misoprostol, vaginal and sublingual routes are equally effective after mifepristone, but there is a greater risk of failure when the dose of misoprostol is 400 micrograms compared with 800 micrograms, and adverse effects are more frequent with sublingual use.[12] The interval between doses of mifepristone and misoprostol is usually 36 to 48 hours, but the use of vaginal misoprostol 24 hours after mifepristone is also effective.[9,12,13] Successful use of vaginal misoprostol with intramuscular or oral methotrexate has also been described.[14–17]

Misoprostol on its own is only a weak abortifacient, particularly when given orally, and congenital malformations have been reported after failed abortion attempts using misoprostol alone (see Effects on the Fetus, p. 2142.2). However, there is interest in finding a regimen that is effective, particularly in countries where mifepristone is unavailable. A dose of 800 micrograms vaginally, repeated after 24 hours, has been suggested for pregnancy of up to 63 days.[18,19] A large study[20] has also reported that 800 micrograms given every 12 hours for 3 doses was less effective when given sublingually than vaginally; the routes were equally effective when misoprostol was given every 3 hours, but sublingual administration caused more adverse effects such as fever, chills, shivering, and diarrhoea.

Misoprostol has also been studied for termination of pregnancy during the *second trimester*. It has been used in various regimens to induce medical termination, given either alone[21–23] or after oral mifepristone,[24,25] and reported to be effective when given vaginally, sublingually, or orally. The time to complete abortion may depend on the dose,

dosage interval, and route of administration. Compared with other prostaglandins, intravaginal misoprostol alone (generally as a single dose of 200 micrograms or repeated after 12 hours if necessary) has been reported to be as effective as dinoprostone for medical termination.[26] Another study[27] found 400 micrograms intravaginally every 3 hours, up to 5 doses, to be at least as effective as intra-amniotic carboprost. The use of buccal misoprostol to prepare the cervix before surgical termination has also been described.[28]

In the management of **early pregnancy loss**, intravaginal misoprostol has been proposed as an alternative to surgery for evacuation of the uterus.[29] Doses have ranged from 400 to 800 micrograms, but the lower doses tend to be less effective.[30] The American College of Obstetricians and Gynecologists has suggested that for women with a uterine size of less than 12 weeks of gestation, an oral dose of misoprostol 600 micrograms may be given for incomplete abortion or miscarriage. For missed miscarriage a dose of 800 micrograms may be given vaginally, or 600 micrograms sublingually, which may be repeated every 3 hours for 2 additional doses.[31] Misoprostol has also been used with mifepristone for uterine evacuation after early pregnancy loss (see Termination of Pregnancy, p. 2139.2).

1. Ngai SW, *et al.* The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: a randomized trial. *Hum Reprod* 1999; 14: 2139–42.
2. Saxena P, *et al.* Comparison between the sublingual and oral route of misoprostol for pre-abortion cervical priming in first trimester abortions. *Hum Reprod* 2004; 19: 77–80.
3. Vimala N, *et al.* Cervical priming with sublingual misoprostol vs. 15-methyl-prostaglandin F2 α prior to surgical abortion. *Int J Gynecol Obstet* 2005; 88: 134–7.
4. Carbonell Esteve JL, *et al.* Sublingual versus vaginal misoprostol (400 micrograms) for cervical priming in first-trimester abortion: a randomized trial. *Contraception* 2006; 74: 328–33.
5. Peyron R, *et al.* Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. *N Engl J Med* 1993; 328: 1509–13.
6. Spitz IM, *et al.* Early pregnancy termination with mifepristone and misoprostol in the United States. *N Engl J Med* 1998; 338: 1241–7.
7. El-Refaey H, *et al.* Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *N Engl J Med* 1995; 332: 983–7.
8. Ashok PW, *et al.* Termination of pregnancy at 9-13 weeks' amenorrhoea with mifepristone and misoprostol. *Lancet* 1998; 52: 542–3.
9. Schaff EA, *et al.* Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: a randomized trial. *JAMA* 2000; 284: 1948–53.
10. Shannon C, *et al.* Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial. *BJOG* 2006; 113: 621–8.
11. Hamoda H, *et al.* A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. *BJOG* 2005; 112: 1102–8.
12. von Hertzen H, *et al.* WHO Research Group on Postovulatory Methods of Fertility Regulation. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. *BJOG* 2010; 117: 1186–96.
13. von Hertzen H, *et al.* WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomised factorial controlled equivalence trial. *BJOG* 2009; 116: 381–9.
14. Creinin MD, *et al.* Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997; 90: 611–16.
15. Carbonell JLL, *et al.* Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1998; 57: 83–8.
16. Borgatta L, *et al.* Early medical abortion with methotrexate and misoprostol. *Obstet Gynecol* 2001; 97: 11–16.
17. Aldrich T, Winikoff B. Does methotrexate confer a significant advantage over misoprostol alone for early medical abortion? A retrospective analysis of 8678 abortions. *BJOG* 2007; 114: 555–62.
18. Philip NM, *et al.* A consensus regimen for early abortion with misoprostol. *Int J Gynecol Obstet* 2004; 87: 281–3.
19. Blanchard K, *et al.* Misoprostol alone for early abortion: an evaluation of seven potential regimens. *Contraception* 2005; 72: 91–7.
20. von Hertzen H, *et al.* WHO Research Group on Postovulatory Methods of Fertility Regulation. Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomised controlled equivalence trial. *Lancet* 2007; 369: 1938–46.
21. Tang OS, *et al.* A prospective randomised comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. *BJOG* 2004; 111: 1001–5.
22. Caliskan E, *et al.* Randomized comparison of 3 misoprostol protocols for abortion induction at 13–20 weeks of gestation. *J Reprod Med* 2005; 50: 173–80. Correction. *ibid.*: 732. [dose]
23. von Hertzen H, *et al.* WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Comparison of vaginal and sublingual misoprostol for second trimester abortion: randomized controlled equivalence trial. *Hum Reprod* 2009; 24: 106–12.
24. Hamoda H, *et al.* A randomized trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13–20 weeks gestation. *Hum Reprod* 2005; 20: 2348–54.
25. Tang OS, *et al.* A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation. *Hum Reprod* 2005; 20: 3062–6.
26. Jain JK, Mishell DR. A comparison of intravaginal misoprostol with prostaglandin E_2 for termination of second-trimester pregnancy. *N Engl J Med* 1994; 331: 290–3.
27. Su L-L, *et al.* A prospective, randomized comparison of vaginal misoprostol versus intra-amniotic prostaglandins for midtrimester termination of pregnancy. *Am J Obstet Gynecol* 2005; 193: 1410–14.
28. Patel A, *et al.* Planned Parenthood Federation of America Buccal Misoprostol Waiver Group. Adequacy and safety of buccal misoprostol for cervical preparation prior to termination of second-trimester pregnancy. *Contraception* 2006; 73: 420–30.
29. Zhang J, *et al.* A comparison of medical management with misoprostol and surgical management for early pregnancy failure. *N Engl J Med* 2005; 353: 761–9.
30. Neilson JP, *et al.* Medical treatment for early fetal death (less than 24 weeks). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 30/06/08).
31. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 427: misoprostol for postabortion care. *Obstet Gynecol* 2009; 113: 465–8. Also available at: http://www.who.int/selection_medicines/committees/expert/17/application/ACOG_ref.pdf (accessed 11/09/09)

Adverse Effects

The commonest adverse effect of misoprostol is diarrhoea. Other gastrointestinal effects include abdominal pain, dyspepsia, flatulence, and nausea and vomiting. Increased uterine contractility and abnormal vaginal bleeding (including menorrhagia and intermenstrual bleeding) have been reported. Other adverse effects include rashes, headache, and dizziness. Hypotension is rarely seen at doses recommended for peptic ulcer disease.

For adverse effects associated with the obstetric and gynaecological use of prostaglandins see under Dinoprostone, p. 2134.3.

Incidence of adverse effects. Data on misoprostol presented to the FDA have been summarised.[1] During controlled studies the most common adverse effect was diarrhoea (8.2% compared with 3.1% for placebo); it was dose-related but usually mild, only 8 of 2003 subjects receiving misoprostol having withdrawn because of incapacitating diarrhoea. Headaches and abdominal discomfort were also reported. The effects of misoprostol on the uterus and the potential risks of uterine bleeding or abortion in pregnant women were of more concern. In non-pregnant women taking part in the controlled studies there were menstrual complaints in 15 of 410 (3.7%) receiving misoprostol compared with 2 of 115 (1.7%) given placebo. In a study in pregnant women who had elected to undergo first trimester abortion, all 6 who had a spontaneous expulsion of the uterine contents had received 1 or 2 doses of misoprostol 400 micrograms the previous evening, while none of those given placebo aborted spontaneously; overall 25 of the 56 women given misoprostol had uterine bleeding compared with only 2 of 55 on placebo.

1. *Lewis JH.* Summary of the 29th meeting of the Gastrointestinal Drugs Advisory Committee, Food and Drug Administration—June 10, 1985. *Am J Gastroenterol* 1985; 80: 743–5.

Effects on the fetus. Misoprostol on its own is only a weak abortifacient and is often ineffective when used alone for the termination of pregnancy (see p. 2141.3). However, it has been widely misused for this purpose in some countries, notably Brazil,[1,2] and anecdotal reports have associated congenital malformations with such misuse during the first trimester of pregnancy. A systematic review[3] of 4 case-control studies confirmed that misoprostol was associated with an increased risk of congenital abnormality, particularly Möbius syndrome and terminal transverse limb defects.

A case of Möbius syndrome has also been reported after a failed termination using the approved regimen of mifepristone followed by misoprostol.[4]

1. Costa SH, Vessey MP. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. *Lancet* 1993; 341: 1258–61.
2. Coêlho HLL, *et al.* Misoprostol and illegal abortion in Fortaleza, Brazil. *Lancet* 1993; 341: 1261–3. Correction. *ibid.*: 1486.
3. da Silva Dal Pizzol T, *et al.* Prenatal exposure to misoprostol and congenital anomalies: systematic review and meta-analysis. *Reprod Toxicol* 2006; 23: 666–71.
4. Bos-Thompson M-A, *et al.* Möbius syndrome in a neonate after mifepristone and misoprostol elective abortion failure. *Ann Pharmacother* 2008; 42: 888–92.

Effects on the uterus. For reference to uterine rupture in women given misoprostol to induce labour or terminate pregnancy, see under Dinoprostone, p. 2135.2.

Toxic shock syndrome. Fatal toxic shock syndrome has occurred in a few women who underwent medical termination of pregnancy using oral mifepristone and vaginal misoprostol, although a causal relationship between these drugs and the deaths has not been established (see under Mifepristone, p. 2140.1).

Precautions

Misoprostol should not be used to treat peptic ulcer disease in patients who are pregnant or who may become pregnant because it can cause uterine contraction. It should be used with caution in patients in whom hypotension might cause severe complications. Patients with conditions such as inflammatory bowel disease, for whom profound diarrhoea could be dangerous, should be monitored carefully if misoprostol is given.

Like other prostaglandins used in the termination of pregnancy (see Dinoprostone, p. 2136.1), misoprostol should not be used in women at increased risk of uterine rupture, such as those with multiple pregnancy or a uterus scarred by previous caesarean section. Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Breast feeding. Misoprostol acid was detected in the breast milk of 10 women given a single oral dose of misoprostol for postpartum uterine atony.[1] The concentration rose rapidly, peaked at about 1 hour, and had fallen towards the detection limit by about 5 hours after the dose. Product information for misoprostol licensed for use in gastric ulceration advises that it should not be given to breast-feeding women because misoprostol acid could potentially cause diarrhoea in the infant.

1. Vogel D, *et al.* Misoprostol versus methylergometrine: pharmacokinetics in human milk. *Am J Obstet Gynecol* 2004; 191: 2168–73.

Inflammatory bowel disease. Life-threatening diarrhoea was reported in a patient with unrecognised Crohn's disease after 6 doses of misoprostol.[1] Abdominal cramps, pain, and profuse watery diarrhoea also occurred after 3 doses of misoprostol in a woman with Crohn's disease.[2] In a cohort study of misoprostol taken with NSAIDs for arthritis there were 13 patients with a history of inflammatory bowel disease; 7 did not develop diarrhoea, 3 developed mild diarrhoea, 1 developed severe diarrhoea that stopped when misoprostol was withdrawn, and 2 developed bloody diarrhoea.[3]

1. Kornbluth A, *et al.* Life-threatening diarrhea after short-term misoprostol use in a patient with Crohn ileocolitis. *Ann Intern Med* 1990; 113: 474–5.
2. Johnson JS, *et al.* Profuse diarrhea after misoprostol use in a patient with a history of Crohn's disease. *Ann Pharmacother* 1992; 26: 1092–3.
3. Faich GA, *et al.* Diarrhea after misoprostol in Crohn disease. *Ann Intern Med* 1991; 114: 342.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies misoprostol as probably not porphyrinogenic when used in the treatment of peptic ulcer disease; it may be used as a drug of first choice and no precautions are needed. A classification is not offered for its use in obstetrics.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/08/11)

Interactions

NSAIDs. It has been suggested that *aspirin* and *NSAIDs*, which are prostaglandin synthetase inhibitors, might alter the efficacy of misoprostol used for termination of pregnancy by inhibiting uterine cramping and cervical ripening. However, studies in women undergoing medical[1] or surgical[2] termination found that NSAIDs did not reduce the efficacy of misoprostol. In another study,[3] *diclofenac* did not reduce the efficacy of medical termination using mifepristone followed by misoprostol.

1. Creinin MD, Shulman T. Effect of nonsteroidal anti-inflammatory drugs on the action of misoprostol in a regimen for early abortion. *Contraception* 1997; 56: 165–8.
2. Li CFL, *et al.* A study of co-treatment of nonsteroidal anti-inflammatory drugs (NSAIDs) with misoprostol for cervical priming before suction termination of first trimester pregnancy. *Contraception* 2003; 67: 101–5 Correction. *ibid.*: 339.
3. Fiala C, *et al.* The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13–22 weeks gestation. *Hum Reprod* 2005; 20: 3072–7.

Pharmacokinetics

Misoprostol is reported to be rapidly absorbed and metabolised to its active form (misoprostol acid; SC 30695) after oral doses; peak plasma concentrations of misoprostol acid occur after about 15 to 30 minutes. Food reduces the rate but not the extent of absorption. Misoprostol acid is further metabolised by oxidation in several body organs and is excreted mainly in the urine. The plasma elimination half-life is reported to be between 20 and 40 minutes. Misoprostol acid is distributed into breast milk.

References.

1. Schoenhard G, *et al.* Metabolism and pharmacokinetic studies of misoprostol. *Dig Dis Sci* 1985; 30 (suppl): 126S–128S.
2. Karim A, *et al.* Effects of food and antacid on oral absorption of misoprostol, a synthetic prostaglandin E_1 analog. *J Clin Pharmacol* 1989; 29: 439–43.
3. Foote EF, *et al.* Disposition of misoprostol and its active metabolite in patients with normal and impaired renal function. *J Clin Pharmacol* 1999; 39: 384–9.
4. Zieman M, *et al.* Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; 90: 88–92.
5. Khan R-U, El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. *Obstet Gynecol* 2003; 101: 968–74.
6. Khan R-U, *et al.* Oral, rectal, and vaginal pharmacokinetics of misoprostol. *Obstet Gynecol* 2004; 103: 866–70.
7. Schaff EA, *et al.* Comparison of misoprostol plasma concentration following buccal and sublingual administration. *Contraception* 2005; 72: 22–5.
8. Aronsson A, *et al.* Pharmacokinetic profiles up to 12 h after administration of vaginal, sublingual and slow-release oral misoprostol. *Hum Reprod* 2007; 22: 1912–18.
9. Tang OS, *et al.* Pharmacokinetics of repeated doses of misoprostol. *Hum Reprod* 2009; 24: 1862–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Cytotec; *Austria*: Cyprostol; *Belg.*: Cytotec; *Braz.*: Cytotec†; *Chile*: Alumbra; Misotrol; *China*: Cytotec (喜克愦); *Denm.*: Cytotec; *Fin.*: Cytotec; *Fr.*: Cytotec; Gymiso; *Gr.*: Cytotec; *Hong Kong*: Cytotec; *India*: Aboprost; Cedate-P; Cytolog; Kontrac; Mesopil; Misobort; Misogest; Misolast; Misolup; Misoprost; Misotol; Mizolast; MS-Kare; *Indon.*: Chromalux; Citrosol; Cytotec; Gastrul; Noprostol; *Irl.*: Cytotec; *Israel*: Cytotec; *Ital.*: Cytotec; Misodex; *Malaysia*: Cytotec; *Mex.*: Cytux; Cytotec; *Neth.*: Cytotec; MisoOne; *Norw.*: Cytotec; *NZ*: Cytotec; *Pol.*: Cytotec; *Port.*: Cytotec; *Rus.*: Cytotec (Сайтотек); Mirolut (Миролют); *S.Afr.*: Cytotec; *Singapore*: Cytotec; Misel; *Spain*: Cytotec; Misofar; *Swed.*: Cytotec; *Switz.*: Cytotec; *Thail.*: Cytotec; *Turk.*: Cytotec; *UK*: Cytotec; Topogyne; *Ukr.*: Mirolut (Миролют); *USA*: Cytotec; *Venez.*: Cytotec.

Multi-ingredient Preparations. *Neth.*: Medabon.

Used as an adjunct in. *Arg.*: Blokium Prost†; Oxaprost; *Austral.*: Arthrotec; *Austria*: Arthrotec; *Belg.*: Arthrotec; *Canad.*: Arthrotec; *China*: Arthrotec (奥斯克); *Denm.*: Arthrotec; *Fin.*: Arthrotec; *Fr.*: Artotec; *Ger.*: Arthrotec; *Gr.*: Arthrotec; *Hong Kong*: Arthrotec; *India*: Mifenac; Misonac; *Irl.*: Arthrotec; *Israel*: Arthrotec; *Ital.*: Artrotec; Misofenac; *Mex.*: Artrenac Pro; Artrene; Artrotec; *Neth.*: Arthrotec; Misofenac†; Normulen†; *Norw.*: Arthrotec; *Pol.*: Arthrotec; *Port.*: Arthrotec; Diclotec†; *Rus.*: Arthrotec (Артротек); *S.Afr.*: Arthrotec; *Spain*: Artrotec; Normulen†; *Swed.*: Arthrotec; *Switz.*: Arthrotec; *Turk.*: Arthrotec; *UK*: Arthrotec; Misofen; Napratec; *USA*: Arthrotec; *Venez.*: Arthrotec.

Oxytocin *(BAN, rINN)*

Alpha-hypophamine; Hipofamina; Ocitocina; Ocytocine; Oksitocinas; Oksitosiini; Oksitosin; Oksytocyna; Ossitocina; Oxitocin; Oxitocina; Oxytocine; Oxytocinum; Oxytósin; Окситоцин.

Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2 cyclic (1→6) disulphide; [2-Leucine,7-isoleucine]vasopressin.

$C_{43}H_{66}N_{12}O_{12}S_2$=1007.2

CAS — 50-56-6.

ATC — H01BB02.

ATC Vet — QH01BB02.

UNII — 1UQ5135EYN.

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

Ph. Eur. 8: (Oxytocin). A cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary that stimulates contraction of the uterus and milk ejection in receptive mammals. It is obtained by chemical synthesis and is available in the freeze-dried form as an acetate. A white or almost white, hygroscopic powder. Very soluble in water and in dilute solutions of dehydrated alcohol and of acetic acid. A 2% solution in water has a pH of 3.0 to 6.0. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Ph. Eur. 8: (Oxytocin Concentrated Solution). A solution of oxytocin with a concentration of not less than 250 micrograms of oxytocin per mL. It may contain a suitable antimicrobial preservative. A clear colourless liquid with a pH of 3.0 to 5.0. Store at 2 degrees to 8 degrees. Protect from light.

USP 36: (Oxytocin). A nonapeptide hormone having the property of causing the contraction of uterine smooth muscle and of the myoepithelial cells within the mammary glands. It is prepared by synthesis. Its oxytocic activity is not less than 400 units/mg. Store in airtight containers at 2 degrees to 8 degrees.

Units

12.5 units of oxytocin for bioassay are contained in about 21.4 micrograms of synthetic peptide (with human albumin 5 mg and citric acid) in one ampoule of the fourth International Standard (1978).

Uses and Administration

Oxytocin is a cyclic nonapeptide secreted by the hypothalamus and stored in the posterior lobe of the pituitary gland. It may be prepared from the gland of mammals or by synthesis.

Oxytocin causes contraction of the uterus, the effect increasing with the duration of pregnancy due to proliferation of oxytocin receptors. Small doses increase the tone and amplitude of the uterine contractions; large or repeated doses result in tetany. Oxytocin also stimulates the smooth muscle associated with the secretory epithelium of the lactating breast causing the ejection of milk but having no direct effect on milk secretion. It has a weak antidiuretic action.

Oxytocin is used for the induction and augmentation of labour, to control postpartum bleeding and uterine hypotonicity in the third stage of labour, and to promote lactation in cases of faulty milk ejection. It is also used as an adjunctive therapy in some types of miscarriage or abortion, but other measures may be preferred.

When given for the induction or augmentation of labour, oxytocin should not be started for 6 hours after vaginal prostaglandins have been given. Oxytocin is given by slow intravenous infusion, preferably by means of an infusion pump, but licensed doses vary between countries and guidelines may also suggest regimens that differ again (see also below). Licensed product information generally recommends using a solution containing 5 units in 500 mL of a physiological electrolyte solution such as sodium chloride 0.9%, but more concentrated solutions may be given via infusion pump. In the UK the infusion may be started at a rate of 1 to 4 milliunits/min, and then gradually increased at intervals of at least 20 minutes until a maximum of 3 or 4 contractions are occurring every 10 minutes. In the USA, licensed dosage recommendations are lower, starting at 0.5 to 1 milliunit/min, and gradually increasing the dose in increments of 1 to 2 milliunits/min at intervals of 30 to 60 minutes. A rate of up to 6 milliunits/min is reported to produce plasma oxytocin concentrations comparable to those in natural labour. About 10 milliunits/min is usually the most that is needed at term, but doses of up to 20 milliunits/min or more may be required in situations such as labour induction at an earlier stage of pregnancy or for intra-uterine fetal death. UK information also suggests that if regular contractions are not established after a total of 5 units then the attempt to induce labour should be stopped. However, it may be repeated on the following day, starting again with a rate of 1 to 4 milliunits/min. Fetal heart rate and uterine contractions should be monitored continuously. Once labour is progressing, oxytocin infusion may be gradually withdrawn.

Oxytocin may be used for the prevention and treatment of **postpartum haemorrhage** (p. 2144.1). In the active management of the third stage of labour, to prevent postpartum haemorrhage, the fixed combination of *Syntometrine* (oxytocin 5 units with ergometrine maleate 500 micrograms) may be given by intramuscular injection after delivery of the anterior shoulder, or, at the latest, immediately after delivery of the infant. The *BNF* suggests a single intramuscular dose of oxytocin 10 units may be used alone, causing less nausea, vomiting, and hypertension than the combination. An alternative for the prevention of postpartum haemorrhage is the administration of oxytocin 5 units by slow intravenous injection, or intramuscular *Syntometrine*, after delivery of the placenta. In women given oxytocin for induction or augmentation of labour, the infusion should be continued at an increased rate during the third stage of labour and for the next few hours thereafter. A single dose of oxytocin 5 units by slow intravenous injection may be given during caesarean section, immediately after delivery of the child.

In the treatment of haemorrhage, oxytocin may be given in a dose of 5 units by slow intravenous injection. This may be followed in severe cases by intravenous infusion of a solution containing 5 to 20 units in 500 mL of a suitable non-hydrating diluent, at a rate that controls uterine atony. The *BNF* suggests that the initial dose of 5 units by slow intravenous injection may be repeated, then followed if necessary in severe cases by an infusion containing 40 units in 500 mL, the rate being adjusted to control atony. A dose of intramuscular *Syntometrine* is another option. In the USA a dose of up to 10 units of oxytocin, by intravenous infusion at a rate of 20 to 40 milliunits/min after delivery of the infant, or as an intramuscular injection after delivery of the placenta, has been used for control of postpartum haemorrhage.

For adjunctive therapy in **incomplete, inevitable, or missed miscarriage** (see Termination of Pregnancy, p. 2131.3) a suggested dose in the UK is 5 units by slow intravenous injection, followed if necessary by intravenous infusion at a rate of 20 to 40 milliunits/min or higher.

Oxytocin nasal spray is used to facilitate **lactation**: a dose of one spray, delivering 4 units, into one nostril 5 minutes before suckling has been used. However, evidence for its efficacy is limited and there is a danger that the mother may become dependent upon its action; such usage is not generally recommended (see p. 2130.1).

An **oxytocin challenge test** (below) has been used to evaluate fetal distress in pregnant patients at high risk.

Synthetic derivatives of oxytocin such as demoxytocin (p. 2133.3) have been used similarly.

Labour induction and augmentation. Oxytocin infusions are used for induction and augmentation of labour, as discussed on p. 2129.1. They are usually used to induce labour in women with ruptured membranes and will reduce the number of women who are undelivered 24 hours after starting therapy. However, oxytocin is less effective than dinoprostone, and caesarean section and epidural analgesia use are more likely with oxytocin than with expectant management.[1]

There have been many studies on the dosage of oxytocin required to induce or augment labour. Various dosage regimens have been tried, and studies have reported using initial doses ranging from 0.5 to 6 milliunits/min, dose increases of 1 to 6 milliunits/min, and intervals between increases of 15 to 40 minutes.[2] However, it has been pointed out that no one regimen has been clearly proved superior.[2-4] Higher doses and shorter intervals between increases can shorten labour and reduce rates of intra-amniotic infection and caesarean delivery, but result in more uterine hyperstimulation and emergency caesarean deliveries for fetal distress.[2] The American College of Obstetricians and Gynecologists has suggested that both low- and high-dose regimens within this range are appropriate for labour induction.[5] WHO[6] suggests a starting dose of 2.5 milliunits/min, increased at intervals of 30 minutes, and titrated against contractions to a maximum of 30 milliunits/min in multigravida and women with previous caesarean scars, or 60 milliunits/min in primigravida. WHO also includes a more rapid dose escalation regimen that may be considered for use in primigravida.

1. Alfirevic Z, *et al.* Intravenous oxytocin alone for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 10/02/11).
2. Stubbs TM. Oxytocin for labor induction. *Clin Obstet Gynecol* 2000; **43**: 489–94.
3. Patka JR, *et al.* High- versus low-dose oxytocin for augmentation or induction of labor. *Ann Pharmacother* 2005; **39**: 95–101.
4. Smith JG, Merrill DC. Oxytocin for induction of labor. *Clin Obstet Gynecol* 2006; **49**: 594–608.
5. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. Induction of labour (practice bulletin number 107, August 2009). *Obstet Gynecol* 2009; **114**: 386–97.
6. WHO. *Managing complications in pregnancy and childbirth: a guide for midwives and doctors.* Geneva: WHO, 2000. Also available at: http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf (accessed 23/08/10)

Lactation induction. Oxytocin has been used to promote milk ejection, but good maternal education and support in techniques that promote physiological lactation remain the most important methods for successful breast feeding (see p. 2130.1). However, intranasal oxytocin might be useful in tetraplegic women, where the suckling-induced stimulation that normally triggers the release of oxytocin from the hypothalamus is impaired, as described in a case report.[1]

1. Cowley KC. Psychogenic and pharmacologic induction of the let-down reflex can facilitate breastfeeding by tetraplegic women: a report of 3 cases. *Arch Phys Med Rehabil* 2005; **86**: 1261–4.

Oxytocin challenge test. The oxytocin challenge test (OCT) is designed to detect placental insufficiency, and identify fetuses at risk of still-birth or complications during labour. Its use has declined with the development of other surveillance methods based on ultrasonography.[1] In a study, it was performed on 399 occasions in 305 women with pregnancies at risk and a gestational age of 36 weeks or more.[2] Oxytocin 1 milliunit/minute was given by infusion pump and increased every 5 to 10 minutes until a contraction rate of 3 per 10 minutes was achieved. Less than 10% of late or variable decelerations of fetal heart rate (FHR) was judged negative; 10 to 29% was judged equivocal; and 30% or more was judged positive. The finding of a positive or equivocal response to the OCT was considered a prediction of decelerations of the FHR during parturition, though the type of risk might vary. After 100 OCTs in 90 pregnant women considered at risk[3] it was concluded that a negative result is a reliable test of fetal well-being which should encourage obstetricians to await spontaneous onset of labour in preference to intervention. However, there have been reports of fetal death occurring despite a negative response to the OCT.[4-6] Another study[7] found that in 239 women with an unequivocal OCT result, a negative response was a reliable test for a good outcome, but that a positive result was not a reliable predictor of poor outcome.

Adverse effects associated with the OCT have included haemorrhage occurring in a patient after the second of two tests (the patient was found to have a major placenta praevia)[8] and neonatal hyperbilirubinaemia.[9] The latter effect led to the suggestion that the OCT should be used with caution in women whose babies might be at risk from hyperbilirubinaemia.

1. Devoe LD. Antenatal fetal assessment: contraction stress test, nonstress test, vibroacoustic stimulation, amniotic fluid volume, biophysical profile, and modified biophysical profile—an overview. *Semin Perinatol* 2008; **32**: 247–52.
2. Schulman H, *et al.* Quantitative analysis in the oxytocin challenge test. *Am J Obstet Gynecol* 1977; **129**: 239–44.
3. Sellappah S, Wagman H. Oxytocin challenge test as an out patient procedure. *Br J Clin Pract* 1984; **38**: 255–8.
4. Marcum RG. False negative oxytocin challenge test. *Am J Obstet Gynecol* 1977; **127**: 894.
5. Lorenz RP, Pagano JS. A case of intrauterine fetal death after a negative oxytocin challenge test. *Am J Obstet Gynecol* 1978; **130**: 232.
6. Dittman R, Belcher J. False-negative oxytocin challenge test. *N Engl J Med* 1978; **298**: 56.
7. Ocak V, *et al.* The predictive value of fetal heart rate monitoring: a retrospective analysis of 2165 high-risk pregnancies. *Eur J Obstet Gynecol Reprod Biol* 1992; **44**: 53–8.

8. Ng KH, Wong WP. Risk of haemorrhage in oxytocin stress test. *BMJ* 1976; 2: 698–9.
9. Peleg D, Goldman JA. Oxytocin challenge test and neonatal hyperbilirubinaemia. *Lancet* 1976; ii: 1026.

Postpartum haemorrhage. Oxytocin is used for the prophylaxis and treatment of postpartum haemorrhage (p. 2130.2). In the active management of the third stage of labour, the combination of oxytocin and ergometrine may be associated with a small reduction in the risk of postpartum haemorrhage compared with oxytocin alone, but a higher incidence of nausea, vomiting, and hypertension.

Oxytocin injected into the vein of the umbilical cord has been used to assist the removal of retained placenta. A meta-analysis[1] of 12 studies found evidence that oxytocin reduced the incidence of manual removal of the retained placenta, although there was no apparent benefit in terms of other measures including blood loss, curettage, and infection. Most studies had used a dose of oxytocin 10 units in 20 mL of sodium chloride 0.9%. In the UK, a dose of 20 units in 20 mL, followed by proximal clamping of the cord, has been recommended.[2] However, a large controlled study (Release study)[3] subsequently found that umbilical injection of oxytocin 50 units in 30 mL was no better than placebo in reducing the need for manual removal of placenta. The authors also updated the previous meta-analysis[1] with this new data and found that there was no statistically significant benefit associated with oxytocin use.

1. Carroli G, Bergel E. Umbilical vein injection for management of retained placenta. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 21/09/09).
2. National Collaborating Centre for Women's and Children's Health/NICE. Intrapartum care: care of healthy women and their babies during childbirth (issued September 2007; corrected June 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG55FullGuideline.pdf (accessed 21/09/09)
3. Weeks AD, *et al.* Umbilical vein oxytocin for the treatment of retained placenta (Release Study): a double-blind, randomised controlled trial. *Lancet* 2010; 375: 141–7.

Adverse Effects

Oxytocin given in high doses, or to women who are hypersensitive to it, may cause uterine hyperstimulation with hypertonic or tetanic contractions, leading to uterine rupture and soft tissue damage. Effects in the fetus include bradycardia, arrhythmias, asphyxiation, and perhaps death.

Maternal deaths from severe hypertension and subarachnoid haemorrhage have occurred. Rapid intravenous injection of oxytocin has produced acute transient hypotension with flushing and reflex tachycardia. Postpartum haemorrhage, fatal afibrinogenaemia, and disseminated intravascular coagulation have been reported, but may be due to complications of labour induction rather than oxytocin itself.

High doses of oxytocin infused over prolonged periods can also cause water retention leading to hyponatraemia and intoxication, which may progress to convulsions, coma, and even death. Vasopressin-like activity (see p. 2643.3) is more likely with oxytocin of natural origin but may occur even with the synthetic peptide.

Other adverse effects include headache, nausea and vomiting, rashes, cardiac arrhythmias, pelvic haematoma, and anaphylactic and other hypersensitivity reactions.

There are reports of neonatal jaundice and retinal haemorrhage associated with the use of oxytocin in the management of labour.

Adverse effects after intranasal use of oxytocin have included nasal irritation, rhinorrhoea, lachrymation, uterine bleeding, and violent uterine contractions.

Inappropriate use. In a 1988 comment on the misuse of oxytocin in labour,[1] it was noted that statements on the management of labour were often misinterpreted as meaning that all women who failed to make adequate progress in terms of cervical dilatation should be given oxytocin. This was only true if poor progress was due to poor uterine action, and would be dangerous where there was disproportion; the decision to use oxytocin required careful assessment by an experienced obstetrician. In the previous 2 years the authors had seen one case of fractured pelvis, 2 of ruptured uterus, and 7 of cerebral palsy from fetal hypoxia, all of which were thought to be due to the ill-advised use of oxytocin to augment labour. More than a decade later the injudicious use of oxytocin during labour, with adverse outcomes including neonatal brain damage and death, continues to be reported. A review[2] of obstetric malpractice claims in Sweden found that the incorrect use of oxytocin was obvious in 37 of 54 cases; often, the oxytocin infusion had been increased despite a non-reassuring fetal heart rate pattern with or without overly frequent uterine contractions, or fetal monitoring was inadequate and hence fetal distress not recognised.

1. Taylor RW, Taylor M. Misuse of oxytocin in labour. *Lancet* 1988; i: 352.
2. Jonsson M, *et al.* Analysis of malpractice claims with a focus on oxytocin use in labour. *Acta Obstet Gynecol Scand* 2007; 86: 315–19.

Neonatal jaundice. Analysis of neonatal jaundice in 12 461 single births confirmed a higher incidence of jaundice in offspring of mothers given oxytocin, independent of gestational age at birth, male sex, Afro-Caribbean, Chinese, or Japanese race, epidural analgesia, ventouse delivery, and birth-weight, which were also associated with jaundice.[1] A later review[2] of 12 023 single births also found some of these factors to be associated with neonatal hyperbilirubinaemia, but not Afro-Caribbean race, epidural analgesia, or the use of oxytocin. Another smaller population study[3] also concluded that oxytocin was not significantly related to neonatal jaundice. In a total of 90 infants born to mothers after oxytocin-induced labour in 2 studies,[4,5] haematological disturbances were noted. These included erythrocyte fragility or reduction in erythrocyte deformability, hyponatraemia, hypo-osmolality, and an increase in serum-bilirubin concentration. Glucose injection, used as a vehicle for oxytocin may have further aggravated these changes.[5] A comparison[6] of women who received oxytocin infusion in either glucose 5% or sodium chloride 0.9% found the use of glucose to be associated with more cases of hyponatraemia in cord plasma, and neonatal hyperbilirubinaemia. In contrast, another study[7] found no difference between these diluents, but did report that neonatal bilirubin concentrations were higher when oxytocin had been used for augmentation of labour, compared with labour induction.

See also under Oxytocin Challenge Test in Uses and Administration, p. 2143.3.

1. Friedman L, *et al.* Factors influencing the incidence of neonatal jaundice. *BMJ* 1978; 1: 1235–7.
2. Linn S, *et al.* Epidemiology of neonatal hyperbilirubinemia. *Pediatrics* 1985; 75: 770–4.
3. Seidman DS, *et al.* Predicting the risk of jaundice in fullterm healthy newborns: a prospective population-based study. *J Perinatol* 1999; 19: 564–7.
4. Buchan PC. Pathogenesis of neonatal hyperbilirubinaemia after induction of labour with oxytocin. *BMJ* 1979; 2: 1255–7.
5. Singhi S, Singh M. Pathogenesis of oxytocin-induced neonatal hyperbilirubinaemia. *Arch Dis Child* 1979; 54: 400–2.
6. Omigbodun AO, *et al.* Effect of saline and glucose infusions of oxytocin on neonatal bilirubin levels. *Int J Gynecol Obstet* 1993; 40: 235–9.
7. Oral E, *et al.* Oxytocin infusion in labor: the effect different indications and the use of different diluents on neonatal bilirubin levels. *Arch Gynecol Obstet* 2003; 267: 117–20.

Water intoxication. Oxytocin-induced water intoxication is most likely to arise as a result of prolonged attempts to empty the uterus in missed abortion or mid-trimester termination of pregnancy, but it has also been described after oxytocin infusion in other conditions including induction of labour.[1] Irrespective of the oxytocin concentration, patients in virtually all the reported cases have received more than 3.5 litres of infused fluid. Convulsions and somnolence associated with hyponatraemia have also been reported in a patient who was drinking more than 5 litres of herbal tea daily while using intranasal oxytocin 8 times or more daily.[2]

Another factor contributing to hyponatraemia is the antidiuretic effect of the pethidine and morphine commonly used for analgesia with oxytocin infusions. Water intoxication usually presents with fits and loss of consciousness but in some cases there may be preceding signs such as raised venous pressure, bounding pulse, and tachycardia. Diagnosis is confirmed by profound hyponatraemia; the mechanism appears to be more complex than simply haemodilution by the infused water. Treatment consists of controlling convulsions and maintaining an airway; oxytocin infusion must be stopped and isotonic, or even hypertonic, saline may be infused. Diuresis may then be assisted with furosemide. The prime objective, however, should be prevention; no patient should receive more than 3 litres of fluid containing oxytocin, and a careful fluid balance record is essential.

1. Feeney JG. Water intoxication and oxytocin. *BMJ* 1982; 285: 243.
2. Mayer-Hubner B. Pseudotumour cerebri from intranasal oxytocin and excessive fluid intake. *Lancet* 1996; 347: 623.

Precautions

Oxytocin should not be given where spontaneous labour or vaginal delivery are liable to harm either the mother or the fetus. This includes significant cephalopelvic disproportion or unfavourable presentation of the fetus, placenta praevia or vasa praevia, placental abruption, cord presentation or prolapse, mechanical obstruction to delivery, fetal distress or hypertonic uterine contractions. It should not be used where there is a predisposition to uterine rupture, as in multiple pregnancy or high parity, polyhydramnios, or the presence of a uterine scar from previous caesarean section. Oxytocin should not be used for prolonged periods in resistant uterine inertia, severe pre-eclampsia, or severe cardiovascular disorders.

When given for induction or enhancement of labour particular care is needed in borderline cephalopelvic disproportion, less severe degrees of cardiovascular disease, and in patients over 35 years of age or with other risk factors. Careful monitoring of fetal heart rate and uterine motility is essential so that dosage of oxytocin can be adjusted to individual response; the drug should be given by intravenous infusion, preferably by means of an infusion pump. Infusion should be stopped immediately if fetal distress or uterine hyperactivity occur.

Over-vigorous labour should be avoided in cases of intrauterine fetal death, or where there is meconium-stained amniotic fluid, because there is a risk of amniotic fluid embolism.

The risk of water intoxication should be borne in mind, particularly when high doses of oxytocin are given over a long time. Infusion volumes should be kept low, and in such circumstances an electrolyte-based infusion fluid should be used rather than glucose solution. Oral fluid intake should be restricted and a fluid balance chart maintained; serum electrolytes should be measured if electrolyte imbalance is suspected.

Oxytocin challenge test. For the suggestion that oxytocin challenge testing should be used with caution in women whose offspring might be at risk of hyperbilirubinaemia, see under Uses and Administration, p. 2143.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxytocin 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 30/07/11)

Interactions

Oxytocin may enhance the vasopressor effects of sympathomimetics. Some inhalational anaesthetics, such as cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and reduce its oxytocic effect; cardiac arrhythmias may occur. Prostaglandins and oxytocin may potentiate the effects of each other on the uterus; the UK licensed product information for oxytocin states that it should not be started for 6 hours after use of vaginal prostaglandins.

Pharmacokinetics

Oxytocin undergoes enzymatic destruction in the gastrointestinal tract but it is rapidly absorbed from the mucous membranes when given intranasally. It is metabolised by the liver and kidneys with a plasma half-life of only a few minutes. Only small amounts are excreted unchanged in the urine.

References.

1. Seitchik J, *et al.* Oxytocin augmentation of dysfunctional labor IV oxytocin pharmacokinetics. *Am J Obstet Gynecol* 1984; 150: 225–8.
2. Perry RL, *et al.* The pharmacokinetics of oxytocin as they apply to labo induction. *Am J Obstet Gynecol* 1996; 174: 1390–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hipofisina; Syntocinon Veracuril; *Austral.*: Syntocinon; *Austria*: Syntocinon; *Belg.* Syntocinon; *Braz.*: Naox; Ocitoc; Orastina; Oxiton; Syntocinon *Chile*: Syntocinon; *China*: Ao Sai Tuo Xing (奥赛托星); *Denm.* Syntocinon; *Fin.*: Syntocinon; *Fr.*: Syntocinon; *Ger.*: Syntocinon; *Hong Kong*: Syntocinon; *India*: Evatocin; Foetocin Genox; Gynotocin; Indox; Labtocin; Nitocin; Oxybro; Oxystar Oxyton; Pitocin; Syntocinon; *Indon.*: Induxin; Oxyla; Pitogin Piton-S; Santocyn; Syntocinon; *Irl.*: Syntocinon; *Ital.*: Syntocinon; *Malaysia*: Syntocinon; Udoxan; *Mex.*: Oxitopisa; Syntocinon; Xitocin; *Neth.*: Syntocinon; *Norw.*: Syntocinon; *NZ* Syntocinon; *Philipp.*: Comxytocin; Estima; Evatocin; Petusin; Lavoxin; NeOxyn; Obcin; Otoxin; Oxitone; *Oxtimon*; *Oxymed* Oxyten; Roxipan; Solvoxine; Syntocinon; Syntox; Tocinox Tranoxy; *Port.*: Syntocinon; *S.Afr.*: Syntocinon; *Singapore* Syntocinon; *Spain*: Syntocinon; *Swed.*: Syntocinon; *Switz.* Syntocinon; *Thai.*: Octocin; *Turk.*: Postuitrin; Syntocinon; *UK* Syntocinon; *USA*: Pitocin; *Venez.*: Syntocinon.

Multi-ingredient Preparations. *Austral.*: Syntometrine; *Hong Kong*: Syntometrine; *Irl.*: Syntometrine; *Malaysia*: Syntometrine; *NZ*: Syntometrine; *S.Afr.*: Syntometrine; *Singapore*: Syntometrine; *UK*: Syntometrine.

Pharmacopoeial Preparations

BP 2014: Ergometrine and Oxytocin Injection; Oxytocin Injection;

USP 36: Oxytocin Injection; Oxytocin Nasal Solution.

Prolactin

Galactin; Galactina; Hormona lactogénica; Hormona luteotrópica; Lactoestimulina; Lactogen; Lactogenic Hormone; Lactógeno; Lactotropin; LMTH; LTH; Luteomammotropic Hormone; Luteotrophic Hormone; Luteotropin; Luteotropina; Mammotropin; Mamotropina; Prolactina; Prolactine; Prolaktiini; Prólaktin; Prolaktin; Prolaktinas; Prolaktyna; Prolattina; Пролактин.

CAS — 9002-62-4; 12585-34-1 (sheep); 56832-36-1 (ox); 9046-05-3 (pig).
UNII — 2558538ZG2.

Profile

Prolactin is a water-soluble protein from the anterior pituitary; it is structurally related to growth hormone (p. 1919.3). In *animals*, prolactin has many actions and is involved in reproduction, parental care, feeding of the young, electrolyte balance, and growth and development. In humans it has a definite role in inducing milk production; oxytocin (p. 2143.1) stimulates milk ejection. Relatively high concentrations of prolactin have been found in amniotic fluid. Placental lactogen has been shown to have prolactin-like activity. Prolactin secretion is stimulated by suckling and, for a few months after delivery, it has an inhibitory effect on the ovaries, acting as a natural contraceptive.

The hypothalamus can both stimulate and inhibit prolactin secretion by the anterior pituitary; the inhibitory influence is predominant and is mediated through a dopaminergic system. Dopamine binds to the lactotrope D_2 receptor to inhibit prolactin synthesis and release. Noradrenaline and gamma-aminobutyric acid are also inhibitory as are dopaminergic drugs such as bromocriptine. Although protirelin (p. 2344.2) has prolactin-releasing activity, there is evidence for the existence of a separate hypothalamic releasing factor (PRF). Prolactin secretion may also be stimulated by methyldopa, metoclopramide, reserpine, opioid analgesics, and phenothiazine or butyrophenone antipsychotics.

Hyperprolactinaemia, which is associated with a variety of other endocrine disorders, is discussed on p. 2252.2.

Prolactin has been given by intramuscular injection in the management of lactation disorders and some forms of menstrual disturbance.

Ritodrine Hydrochloride

(BANM, USAN, rINNM) ⊗

DU-21220 (ritodrine); Hidrocloruro de ritodrina; Ritodrin Hidroklorür; Ritodrina, hidrocloruro de; Ritodrine, Chlorhydrate de; Ritodrini Hydrochloridum; Ритодрина Гидрохлорид.

erythro-2-(4-Hydroxyphenethylamino)-1-(4-hydroxyphenyl) propan-1-ol hydrochloride.

$C_{17}H_{21}NO_3HCl$=323.8

CAS — 26652-09-5 (ritodrine); 23239-51-2 (ritodrine hydrochloride).
ATC — G02CA01.
ATC Vet — QG02CA01.
UNII — ESJ56Q60GC.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Ritodrine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in dehydrated alcohol; practically insoluble in acetone and in ether. A 2% solution in water has a pH of 4.5 to 6.0. Store in airtight containers.

USP 36: (Ritodrine Hydrochloride). A white to nearly white, odourless or practically odourless, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in ether; soluble in propyl alcohol. pH of a 2% solution in water is between 4.5 and 6.0. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Ritodrine hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has general properties similar to those of salbutamol (see p. 1220.2). It decreases uterine contractility and is used to arrest premature labour (p. 2131.1).

Ritodrine hydrochloride is usually given by intravenous infusion. Where possible this should be with the aid of a **syringe pump**, when the concentration should be 3 mg/mL, using glucose 5% as the diluent. A recommended initial rate of infusion is 50 to 100 micrograms/min, increased at intervals of 10 to 20 minutes by increments of 50 micrograms/min until there is evidence of patient response. The lowest effective dose should be used for maintenance, which is usually around 50 to 100 micrograms/min. If no syringe pump is available then the infusion may be made using a **controlled infusion device** to deliver a more dilute solution of 300 micrograms/mL, with glucose 5% being used once again as the diluent. The same dose is used as with the syringe pump.

The maternal pulse should be monitored throughout the infusion and the rate adjusted to avoid a maternal heart rate of more than 120 beats/min. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema. Therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions under Salbutamol, p. 1222.3).

Oral or rectal $beta_2$ agonist therapy is no longer recommended in premature labour, because of a lack of evidence of benefit from treatment given by these routes of administration. Formerly, ritodrine hydrochloride could be given orally in a dose of 10 to 20 mg every 4 to 6 hours, to a maximum daily dose of 120 mg, for maintenance therapy after uterine contractions were controlled by parenteral treatment.

Reviews.
1. Yaju Y, Nakayama T. Effectiveness and safety of ritodrine hydrochloride for the treatment of preterm labour: a systematic review. *Pharmacoepidemiol Drug Safety* 2006; 15: 813–22.

Adverse Effects and Precautions

As for Salbutamol Sulfate, p. 1221.3. Leucopenia or agranulocytosis has been reported occasionally with prolonged intravenous use.

In women given ritodrine for premature labour, the risk of pulmonary oedema means that extreme caution is required and the precautions and risk factors discussed under Salbutamol Sulfate, p. 1222.3, apply.

Effects on the eyes. Ritodrine and to a lesser extent salbutamol have been implicated in retinopathy in the premature infant when used for premature labour.[1]

1. Michie CA, *et al.* Do maternal β-sympathomimetics influence the development of retinopathy in the premature infant? *Arch Dis Child* 1994; 71: F149.

Effects on the heart. Myocardial ischaemia or signs of myocardial ischaemia have been reported in patients given ritodrine.[1-3] Sinus tachycardia and ST-segment depression commonly occur in patients given ritodrine, but the relationship between these changes and ischaemia remains unclear.[3]

1. Brosset P, *et al.* Cardiac complications of ritodrine in mother and baby. *Lancet* 1982; ii: 1468.
2. Ben-Shlomo I, *et al.* Myocardial ischaemia during intravenous ritodrine treatment: is it so rare? *Lancet* 1986; ii: 917–18.
3. Verhaert D, Van Acker R. Acute myocardial infarction during pregnancy. *Acta Cardiol* 2004; 59: 331–9.

Effects on skeletal muscle. Elevated serum-creatine kinase concentrations have been found in women given ritodrine tocolysis,[1] and there have been rare reports of rhabdomyolysis.[1,2]

1. Matsuda Y, *et al.* Evaluation of creatine kinase level during long-term tocolysis. *J Perinat Med* 2002; 30: 476–9.
2. Nasu K, *et al.* Rhabdomyolysis caused by tocolysis with oral ritodrine hydrochloride in a pregnant patient with myotonic dystrophy. *Gynecol Obstet Invest* 2006; 61: 53–5.

Pulmonary oedema. Several cases of pulmonary oedema have been reported in patients given a $beta_2$ agonist, including ritodrine, for premature labour.[1-4] In 1995 the UK CSM[4] commented that it had received 10 reports of pulmonary oedema, fatal in 2 patients. The CSM considered that fluid overload was the most important predisposing factor. Other risk factors included multiple pregnancies, a history of cardiac disease, and maternal infection. For further discussion of the precautions necessary in the use of $beta_2$ agonists to treat premature labour, and the risk factors involved, see Salbutamol, p. 1222.3.

1. Hawker F. Pulmonary oedema associated with β_2-sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; 12: 143–51.
2. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med* 1989; 110: 714–18.
3. Clesham GJ, *et al.* β Adrenergic agonists and pulmonary oedema in preterm labour. *BMJ* 1994; 308: 260–2.
4. CSM/MCA Reminder: ritodrine and pulmonary oedema. *Current Problems* 1995; 21: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 30/06/08)

Interactions

As for Salbutamol Sulfate, p. 1223.1.

Pharmacokinetics

Ritodrine is rapidly absorbed from the gastrointestinal tract but is subject to fairly extensive first-pass metabolism; about 30% of an oral dose is bioavailable. It is metabolised in the liver mainly by conjugation with glucuronic acid or sulfate and excreted in urine as unchanged drug and metabolites. About 70 to 90% of a dose is reported to be excreted in the urine within 10 to 12 hours. It crosses the placenta.

References.
1. Gandar R, *et al.* Serum level of ritodrine in man. *Eur J Clin Pharmacol* 1980; 17: 117–22.
2. Gross AS, Brown KP. Plasma protein binding of ritodrine at parturition and in nonpregnant women. *Eur J Clin Pharmacol* 1985; 28: 479–81.
3. Kuhnert BR, *et al.* Ritodrine pharmacokinetics. *Clin Pharmacol Ther* 1986; 40: 656–64.
4. Caritis SN, *et al.* Pharmacokinetics of orally administered ritodrine. *Am J Obstet Gynecol* 1989; 161: 32–5.
5. Caritis SN, *et al.* Pharmacokinetics of ritodrine administered intravenously: recommendations for changes in the current regimen. *Am J Obstet Gynecol* 1990; 162: 429–37.
6. Caritis SN, *et al.* Pharmacokinetics and pharmacodynamics of ritodrine after intramuscular administration to pregnant women. *Am J Obstet Gynecol* 1990; 162: 1215–19.
7. Pacifici GM, *et al.* Sulphation and glucuronidation of ritodrine in human foetal and adult tissues. *Eur J Clin Pharmacol* 1993; 44: 259–64.
8. Pacifici GM, *et al.* Ritodrine sulphation in the human liver and duodenal mucosa: interindividual variability. *Eur J Drug Metab Pharmacokinet* 1998; 23: 67–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ritopar; *Belg.*: Pre-Par; *Braz.*: Miodrina; *China*: Anpo (安宝); *Gr.*: Miolene; Pre-Par; Yutopar; *India*: Miolene; Yutopar; *Indon.*: Yutopar; *Ital.*: Miolene; *Spain*: Pre-Par; *Turk.*: Pre-Par; *UK*: Yutopar†.

Pharmacopoeial Preparations
BP 2014: Ritodrine Injection; Ritodrine Tablets;
USP 36: Ritodrine Hydrochloride Injection; Ritodrine Hydrochloride Tablets.

Sulprostone *(USAN, rINN)*

CP-34089; 16-Phenoxy-ω-17,18,19,20-tetranor-prostaglandin E_2-methylsulfonylamide; SHB-286; Sulproston; Sulprostona; Sulprostoni; Sulprostonum; ZK-57671; Сульпростон.

(*Z*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4-phenoxybut-1-enyl]-5-oxocyclopentyl}-*N*-(methylsulphonyl)hept-5-enamide.

$C_{23}H_{31}NO_7S$=465.6

CAS — 60325-46-4.
ATC — G02AD05.
ATC Vet — QG02AD05.
UNII — 501Q5EQ1GM.

Uses and Administration

Sulprostone is a synthetic derivative of dinoprostone (prostaglandin E_2; p. 2134.1) that has uterine stimulant effects. It is used for dilatation of the cervix before surgical termination of pregnancy in the first trimester, for medical termination of pregnancy in the first or second trimester (p. 2131.3), and to empty the uterus in missed miscarriage, hydatidiform mole, and intra-uterine fetal death. It is also used to control postpartum haemorrhage (p. 2130.2) that has not responded to oxytocin.

Sulprostone is given by intravenous infusion. A dose of 500 micrograms over 3 to 6 hours is used for cervical dilatation in the first trimester. For medical termination of pregnancy in the first or second trimester, or to empty the uterus, sulprostone is infused at a rate of 100 micrograms/hour for up to 10 hours; if necessary the infusion rate may be increased to up to 500 micrograms/hour, to a maximum total dose of 1.5 mg in 24 hours. If termination is unsuccessful the course may be repeated once, 12 to 24 hours after the end of the first infusion.

To control postpartum haemorrhage, an initial infusion of 100 micrograms/hour is given. This may be increased to 500 micrograms/hour if necessary to control bleeding, then reduced to a maintenance dose of 100 micrograms/hour. A total dose of 1.5 mg in 24 hours should not be exceeded.

Sulprostone has also been given extra-amniotically and locally into the cervix. It has also been given by the intramuscular route, but this is no longer recommended.

Adverse Effects and Precautions

As for Dinoprostone, p. 2134.3 and p. 2136.1, respectively. In some countries, such as France, the licensed product information for sulprostone contra-indicates its use for dilatation of the cervix before first trimester surgical termination of pregnancy in smokers or those who have smoked in the last 2 years, and in women over 35 years of age. In these women, methods with a lower risk of cardiovascular adverse effects should be used.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Effects on the cardiovascular system. A 31-year-old woman died from cardiovascular shock during an abortion induced by mifepristone followed by sulprostone. She had

12 children, one previous abortion, and was a heavy cigarette smoker.[1] Four other deaths with sulprostone had not been associated with abortion. Other reported cases that did not result in death have included myocardial infarction in a 32-year-old woman given sulprostone for intrauterine fetal death,[2] and cardiac arrest in a 38-year-old woman, with no history of smoking, after sulprostone was given by both intramyometrial and intravenous bolus injection for postpartum haemorrhage;[3] in both cases the authors suggested that sulprostone had caused coronary artery spasm.

Inadvertent subcutaneous infusion of sulprostone was thought to have caused arterial spasm with pain and oedema in the arm of a woman being treated for postpartum haemorrhage; she recovered after treatment with iloprost infusion.[4]

1. Anonymous. A death associated with mifepristone/sulprostone. *Lancet* 1991; 337: 969–70.
2. Fliers E, *et al.* A prostaglandin analogue as a probable cause of myocardial infarction in a young woman. *BMJ* 1991; 302: 416.
3. Chen FG, *et al.* Cardiac arrest associated with sulprostone use during caesarean section. *Anaesth Intensive Care* 1998; 26: 298–301.
4. de Koning YWCM, *et al.* Critical limb ischemia after accidental subcutaneous infusion of sulprostone. *Eur J Obstet Gynecol Reprod Biol* 1995; 61: 171–3.

Effects on the nervous system. For a report of convulsions in epileptic patients given sulprostone, see under Dinoprostone, p. 2135.2.

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including sulprostone, for termination of pregnancy or induction of labour, see under Dinoprostone, p. 2135.2.

Pulmonary oedema. A 35-year-old woman was given a sulprostone infusion, at a rate varying from 126 to 492 micrograms/hour, as part of the emergency management of postpartum haemorrhage;[1] her religious beliefs prohibited the use of blood products but she was given fluid replacement with lactated Ringer's solution and etherified starches and underwent procedures to control blood loss. However, during recovery, the patient developed pulmonary oedema that the authors suspected to be due to the infusion rate of sulprostone as well as the total dose given (about 600 micrograms).

1. Hagenaars M, *et al.* Pulmonary oedema after high infusion rate of sulprostone. *Br J Anaesth* 2009; 102: 281–2.

Interactions

As for Dinoprostone, p. 2136.1. Sulprostone should not be given with oxytocin or methylergometrine because of the increased risk of tachycardia and coronary vasoconstriction fatalities have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Nalador; *Fr.*: Nalador *Ger.*: Nalador; *Hong Kong*: Nalador†; *Hung.*: Nalador; *Ital.* Nalador; *Neth.*: Nalador; *Port.*: Nalador; *Switz.*: Nalador; *Thai.* Nalador.

Pesticides and Repellents

Pediculosis, p. 2147
Scabies, p. 2148
Vector control, p. 2148

This chapter describes compounds used as pesticides and as insect repellents. The term pesticide covers fungicides, herbicides, insecticides (including acaricides), molluscicides, and rodenticides, among others. Most of the pesticides included here are used in clinical or veterinary practice or in vector control against human or animal disease. Some are used mainly in an agricultural or horticultural setting and are included because of their potential toxicity.

Pesticides can be absorbed during application, by consumption of treated or contaminated products or by accidental contamination, and they may be stored or retained in the tissues. International regulations and controls operate to reduce the risk to both public and user. Values for acceptable daily intakes of pesticides have been published by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) through the WHO Technical Report series of publications or through *Pesticides Residues in Food: yearly evaluations*, FAO Plant Production and Protection Papers, Rome.

Classification of the main pesticides included in this chapter is given in Table 1, below.

The **fungicides** included in this chapter are some of those used in the management of plant disease.

Herbicides are used for weed control both in the domestic setting and professionally in agriculture and horticulture. Those included here may be toxic and have been associated with cases of poisoning.

Insect repellents can help to avoid insect bites and the unpleasant reactions they may produce. Perhaps more importantly, the correct use of insect repellents plays a major role in personal protection against some communicable diseases transmitted by insect vectors. Examples are babesiosis (ticks), Lyme disease (ticks), malaria (mosquitoes), relapsing fevers (lice and ticks), spotted fevers (ticks), and typhus fever (fleas, lice, and mites). Some compounds, such as diethyltoluamide, dimethyl phthalate, and icaridin, are effective as repellents while others, such as benzyl benzoate and some of the pyrethroids, are effective both as repellents and as insecticides.

Insecticides have many applications. They are used in the treatment of ectoparasitic infections such as pediculosis (lice infections) (below) and in the vector control (p. 2148.1) of some communicable diseases that are spread by insects. Acaricides are used to treat scabies (mite infections) (see, p. 2148.1) and are included within the broad classification of insecticides, although acari (mites) are not, technically, insects. Insecticides are also widely used in veterinary practice and in agriculture and horticulture.

The insecticides used in veterinary practice are often classified as topical or systemic ectoparasiticides. Topical ectoparasiticides are applied topically to the host animal (such as dogs or cats) to kill its ectoparasites (such as fleas). In the case of systemic ectoparasiticides the term 'systemic' refers to the ingestion of the insecticide by the ectoparasite from the host's blood; the insecticide may be present in the host's blood either as a result of absorption through the skin after topical application or after systemic dosage.

Molluscicides are used in agriculture or horticulture or in the domestic garden to control snail and slug pests. Additionally, molluscicides such as niclosamide (described in the Anthelmintics chapter on p. 161.2) are used against the freshwater snail vector *Bulinus* in the control of schistosomiasis.

Rodenticides may be used to exterminate rats and mice, which may be vectors for diseases such as leptospirosis, plague, rat-bite fever, and some haemorrhagic fevers. Many rodenticides are anticoagulants. Warfarin (p. 1526.3) is a commonly used rodenticide.

Table 1. Classification of pesticides.

Fungicides	Benomyl, cicloheximide, copper naphthenate, hexachlorobenzene, pentachlorophenol, pyraclostrobin
Herbicides	Dichlorophenoxyacetic acid, dinitro-*o*-cresol, dinitrophenol, diquat, glyphosate, paraquat, pentachlorophenol, trichlorophenoxyacetic acid
Insect repellents	Butopyronoxyl, dibutyl phthalate, diethyltoluamide, dimethyl phthalate, dioctyl adipate, ethohexadiol, piperonal
Insecticides	
Carbamate	Bendiocarb, carbaryl, carbosulfan, methomyl, propoxur
Chlorinated	Chlordane, clofenotane, dieldrin, endosulfan, endrin, heptachlor, lindane, methoxychlor
Organophosphorus	Azamethiphos, bromophos, chlorpyrifos, clofenvinfos, coumafos, cythioate, dichlorvos, dimethoate, dimpylate, dioxation, ethion, famphur, fenitrothion, fenthion, heptenophos, iodofenphos, malathion, naled, parathion, phosmet, phoxim, pirimiphos-methyl, propetamphos, pyraclofos, temefos
Pyrethroid	Alpha-cypermethrin, bioallethrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, esdepallethrine, etofenprox, fenvalerate, flumethrin, permethrin, phenothrin, pyrethrum flower, resmethrin, tetramethrin
Miscellaneous	Amitraz, benzyl benzoate, chloropicrin, copper oleate, cymiazole, cyromazine, diflubenzuron, emamectin, ethylene dibromide, ethylene dichloride, fipronil, fluazuron, fluvalinate, lufenuron, methoprene, methyl bromide, pyriproxyfen, rotenone, sulfiram, triflumuron
Molluscicides	Endod, metaldehyde, pentachlorophenol
Rodenticides	Aluminium phosphide, antu, brodifacoum, bromadiolone, chloralose, chlorophacinone, coumatetralyl, difenacoum, diphenadione, flocoumafen, fluoroacetamide, norbormide, red squill, sodium fluoroacetate

The symbol † denotes a preparation no longer actively marketed

Clinical Uses of Pesticides and Repellents

Pediculosis

Two species of louse cause pediculosis[1-3] in man; these are *Pediculus humanus* with its two varieties, *Pediculus humanus capitis* (the head louse) and *Pediculus humanus humanus* (the body louse), and *Pthirus pubis* (*Phthirus pubis*) (the pubic or crab louse). Unlike the head louse, the body louse is an important vector for infections such as epidemic typhus (p. 212.3), trench fever (p. 210.2), and relapsing fever (p. 202.2).

Insecticides used in the treatment of head lice include the organophosphate malathion, and some pyrethroids such as bioallethrin, permethrin, phenothrin, and tetramethrin. The carbamate, carbaryl, is also effective, although there has been some concern over a theoretical risk of carcinogenicity. Lindane has been used but is no longer recommended as a first-line treatment due to its neurotoxicity and resistance. To be effective, insecticide products need to be applied correctly; a quantity of 50 to 100 mL should be applied thoroughly to the hair from hair root to the tip and left on for 8 to 12 hours. Insecticide products (with the exception of spinosad, see below) kill only adult lice and not the ova (nits), therefore treatment is usually repeated 7 days later. Close contacts should be screened and if infected with living lice should also receive treatment. The insecticide spinosad, derived from the fermentation of *Saccharopolyspora spinosa*, is also used and has been effective in treating permethrin-resistant head lice.[4] Unlike other insecticides, it only needs to be left on the hair for 10 minutes; it is also ovicidal and a second application is only needed if live lice are seen after 7 days.

Resistance has been reported to many of the currently used insecticides. Resistance is considered to be most likely to pyrethroids, intermediate to malathion, and least likely to carbaryl. In the UK the policy of rotating insecticides on a district-wide basis in order to overcome the development of resistance is considered outdated. The current recommendation in the case of suspected resistance and treatment failure is to use an insecticide from a different class for the next course. Lotions are preferred to shampoos for head lice since contact time with the insecticide is longer and treatment is thus more effective. A head louse repellent containing piperonal is available. *Non-insecticide* treatments include a 4% dimeticone lotion[5,6] (see p. 2209.3), 5% benzyl alcohol lotion (see p. 1739.3), 0.5% ivermectin lotion (see p. 155.1), and wet-combing (also called 'bug-busting') with conditioner.[6] Dimeticone is thought to act by disrupting the ability of the lice to manage their water balance. Dimeticone and benzyl alcohol are applied similarly to the insecticide products, although some products have a shorter application time; 2 treatments are also required to kill any newly hatched nymphs. Repeat treatment is not needed with ivermectin lotion. A dry-on, suffocation-based pediculicide has also been claimed to be effective,[7,8] although some have questioned the claims.[9] (Benzyl alcohol is also thought to act by asphyxiation.[10]) Oral ivermectin has been used for refractory infestations.[11] Six methods of delivering hot air at a minimum mean temperature of 55 degrees, for 30 minutes, have been tried and all of them resulted in a high egg mortality rate (greater than or equal to 88%), but showed more variable success in killing the hatched head lice.[12] Guidelines for the management of head lice are available in the UK[13] and in the USA a clinical report on head lice provides guidance and recommendations.[14]

Infestations of crab lice and body lice respond to the same insecticides as head lice. Guidelines for the management of pubic lice are available in the UK.[15] Aqueous solutions are generally preferred to alcoholic for crab louse infestations, since the latter may irritate excoriated skin and genitalia.

Malathion or permethrin have also been suggested for treatment of infestation of the eyelashes and brows with pubic lice (pthiriasis or phthiriasis palpebrarum). Other treatments have included the application of a thick layer of yellow soft paraffin or application of yellow mercuric oxide 1% eye ointment twice daily for about 7 or 8 days or a single application of fluorescein eye drops.

Body louse infestations in the developed world are mainly seen in homeless individuals, and often respond to the provision of opportunities for simple hygiene. Clothing and bed linen of persons with body lice should be washed at high temperature or dry cleaned or treated with insecticides.

There is some evidence that oral ivermectin may be effective in killing body lice.

Topical or systemic antimicrobials should be given as necessary for secondary infections.

1. Elston DM. Drugs used in the treatment of pediculosis. *J Drugs Dermatol* 2009; 8: 207–11.
2. Chuard C. Les pédiculoses. *Rev Med Suisse* 2007; 3: 2266–72.
3. Leone PA. Scabies and pediculosis pubis: an update of treatment regimens and general review. *Clin Infect Dis* 2007; 44 (suppl 3): S153–S159.
4. Cole SW, Lundquist LM. Spinosad for treatment of head lice infestation. *Ann Pharmacother* 2011; 45: 954–9.
5. Pearlman DL. A simple treatment for head lice: dry-on, suffocation-based pediculicide. *Pediatrics* 2004; 114: e275–e279.
6. Burgess IF, *et al.* Treatment of head louse infestation with 4% dimeticone lotion: randomised controlled equivalence trial. *BMJ* 2005; 330: 1423–5.
7. Hill N, *et al.* Single blind, randomised, comparative study of the Bug Buster kit and over the counter pediculicide treatments against head lice in the United Kingdom. *BMJ* 2005; 331: 384–6.
8. Pearlman D. Cetaphil cleanser (Nuvo lotion) cures head lice. *Pediatrics* 2005; 116: 1612.
9. Roberts RJ, Burgess IF. New head-lice treatments: hope or hype? *Lancet* 2005; 369: 8–10.
10. Meinking TL, *et al.* The clinical trials supporting benzyl alcohol lotion 5% (Ulesfia): a safe and effective topical treatment for head lice (pediculosis humanus capitis). *Pediatr Dermatol* 2010; 27: 19–24.
11. Chosidow O, *et al.* Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med* 2010; 362: 896–905. Correction. *ibid.*: 1647.
12. Goates BM, *et al.* An effective nonchemical treatment for head lice: a lot of hot air. *Pediatrics* 2006; 118: 1962–70.
13. Public Health Medicine Environmental Group. Head lice: evidence-based guidelines based on the Stafford Report 2012 update. Available at: http://www.phmeg.org.uk/index.php/download_file/view/92/232/% 20-(accessed 29/03/12)
14. Frankowski BL, Bocchini JA. Council on School Health and Committee on Infectious Diseases. Head lice. *Pediatrics* 2010; 126: 392–403. Also available at: http://pediatrics.aappublications.org/cgi/reprint/126/2/392 (accessed 04/08/10)
15. Clinical Effectiveness Group, British Association of Sexual Health and HIV. United Kingdom national guideline on the management of *Phthirus pubis* infestation (2007). Available at: http://www.bashh.org/documents/28/28.pdf (accessed 28/05/10)

Scabies

Scabies is a parasitic infection of the skin by the mite *Sarcoptes scabiei*. The main symptom is pruritus, which is caused by an allergic reaction to the parasite and may not occur until several weeks after infection for the first time. Subsequent infections usually result in pruritus after a few days. Pruritus may persist for some months after effective treatment with an acaricide, but is not necessarily an indication for further acaricidal treatment; rather, antipruritics should be used. A severe crusted form (Norwegian scabies) may occur rarely, particularly in immunocompromised or incapacitated patients.

Treatment is with the acaricides permethrin or malathion applied, preferably as aqueous lotions, to clean, cool, dry skin over the entire body and left on for 8 to 24 hours, depending upon the preparation. The preparation should be reapplied to the hands whenever they are washed during this period. In adults, it is not usually necessary to treat the face and scalp, but these areas should be treated in young children or patients with atypical or crusted scabies. A single treatment may be effective, but treatment is usually repeated after 7 to 10 days if necessary. Other drugs used topically in the treatment of scabies include benzyl benzoate, crotamiton, lindane, and sulfur; sulfiram is used with benzyl benzoate. Oral ivermectin is an effective alternative. Close family and personal contacts should be treated at the same time and all clothes, towels, and bedding used by the infected person 2 days before treatment should be washed in hot water and dried in a hot dryer.

In addition to treatment with an acaricide, symptomatic treatment of the itching with crotamiton, calamine lotion, or systemic antihistamines or corticosteroids may be required.

References.

1. Elgart ML. A risk-benefit assessment of agents used in the treatment of scabies. *Drug Safety* 1996; 14: 386–93.
2. Chosidow O. Scabies and pediculosis. *Lancet* 2000; 355: 819–26.
3. Roos TC, *et al.* Pharmacotherapy of ectoparasitic infections. *Drugs* 2001; 61: 1067–88.
4. Chosidow O. Scabies. *N Engl J Med* 2006; 354: 1718–27.
5. Heukelbach J, Feldmeier H. Scabies. *Lancet* 2006; 367: 1767–74.
6. Strong M, Johnstone PW. Interventions for treating scabies. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/09/07).
7. Clinical Effectiveness Group, British Association of Sexual Health and HIV. United Kingdom national guideline on the management of scabies infestation (2007). Available at: http://www.bashh.org/documents/27/27.pdf (accessed 28/05/10)
8. Currie BJ, McCarthy JS. Permethrin and ivermectin for scabies. *N Engl J Med* 2010; 362: 717–25.

Vector control

Many pests are involved in the transmission of communicable diseases, and vector control[1,2] is an important part of the fight against such diseases. Insecticides are used in the control of:

- filariasis (p. 146.3) (*Aedes*, *Anopheles*, *Culex*, and *Mansonia* mosquitoes)[3]
- leishmaniasis (p. 922.1) (*Phlebotomus* or *Lutzomyia* sandflies)[4]
- malaria (p. 644.1) (*Anopheles* mosquitoes)[5–8]
- dengue fever (see Haemorrhagic Fevers, p. 952.1) (*Aedes* mosquitoes)[9,10]
- onchocerciasis (p. 147.2) (*Simulium* blackflies)[11]
- African trypanosomiasis (p. 925.2) (*Glossina* tsetse flies)[12]
- American trypanosomiasis (p. 925.3) (*Triatoma* bugs)[13]

The insecticide temefos is useful in dracunculiasis (p. 145.1) (crustacean host to the guinea worm larvae). In some cases, as in filariasis or onchocerciasis, the insecticides used act mainly against the larval stage of the insect vector, whereas in other situations, as in malaria, activity is against the adult insect; in trypanosomiasis, activity is directed against both adult and immature stages. The majority of the experience gained in insecticidal vector control has probably been in malaria, and, for instance, a positive effect seen in the control of leishmaniasis has been considered to be mainly a byproduct of the concomitant malaria control programmes.

Insect repellents can provide personal protection against many insect vectors. For example, in malaria, insect repellents as well as the use of insecticides are important in preventing mosquito bites.

Molluscicides are used in the control of schistosomiasis (p. 148.1) (*Bulinus* snails).[14]

Rodenticides are also extremely valuable in the vector control of some diseases such as leptospirosis (p. 189.3), plague (p. 199.3), rat-bite fever (p. 174.2), and some haemorrhagic fevers (p. 952.1).

1. Chavasse DC, Yap HH, eds. *Chemical methods for the control of vectors and pests of public health importance*. Geneva: WHO, 1997.
2. Rozendaal JA. *Vector control: methods for use by individuals and communities*. Geneva: WHO, 1997.
3. WHO. Lymphatic filariasis: the disease and its control. *WHO Tech Rep Ser 821* 1992. Available at: http://libdoc.who.int/trs/WHO_TRS_821.pdf (accessed 21/07/08)
4. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 21/07/08)
5. WHO. Vector control for malaria and other mosquito-borne diseases. *WHO Tech Rep Ser 857* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_857.pdf (accessed 21/07/08)
6. WHO. *Malaria vector control: insecticides for indoor residual spraying*. Geneva: WHO, 2001.
7. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 18/08/05).
8. WHO. *International travel and health*. 2011 ed. Available at: http://www.who.int/ith/ (accessed 08/07/11)
9. WHO. *Prevention and control of dengue and dengue haemorrhagic fever: comprehensive guidelines*. New Delhi: WHO, 1999. Also available at: http://www.searo.who.int/LinkFiles/Regional_Guidelines_on_Dengue_DHF_prevention_&_control_searo-29.pdf (accessed 10/10/05)
10. Lloyd LS. *Best practices for dengue prevention and control in the Americas*. Washington DC: Environmental Health Project, 2003. Also available at: http://www.ehproject.org/PDF/Strategic_papers/SR7-BestPractice.pdf (accessed 10/10/05)
11. WHO. Report of a WHO expert committee on onchocerciasis control. *WHO Tech Rep Ser 852* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_852.pdf (accessed 21/07/08)
12. WHO. Control and surveillance of African trypanosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 881* 1998. Available at: http://libdoc.who.int/trs/WHO_TRS_881.pdf (accessed 21/07/08)
13. WHO. Control of Chagas disease: second report of the WHO expert committee. *WHO Tech Rep Ser 905* 2002. Available at: http://libdoc.who.int/trs/WHO_TRS_905.pdf (accessed 21/07/08)
14. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 21/07/08)

Aluminium Phosphide

Aluminum Phosphide; Fosfuro de aluminio; Фосфористый Алюминий; Фосфид Алюминия.

AlP=57.96

CAS — 20859-73-8 (aluminium phosphide); 7803-51-2 (phosphine); 1314-84-7 (zinc phosphide).

UNII — E23DR6L59S.

Profile

Aluminium phosphide is used for the fumigation of grain and as a rodenticide. It releases phosphine (PH_3) in the presence of moisture and this accounts for its pesticidal activity. Phosphine gas has a garlic-like odour repulsive to man and domestic animals but apparently not to *rats*. Zinc phosphide is used similarly.

References[1–9] to poisoning associated with aluminium phosphide.

1. Wilson R, *et al.* Acute phosphine poisoning aboard a grain freighter. *JAMA* 1980; 244: 148–50.
2. Singh S, *et al.* Aluminium phosphide ingestion. *BMJ* 1985; 290: 1110–11.
3. Anger F, *et al.* Fatal aluminium phosphide poisoning. *J Anal Toxicol* 2000; 24: 90–2.
4. Nocera A, *et al.* Dangerous bodies: a case of fatal aluminium phosphide poisoning. *Med J Aust* 2000; 173: 133–5.
5. Popp W, *et al.* Phosphine poisoning in a German office. *Lancet* 2002; 359: 1574.
6. Bogle RG, *et al.* Aluminium phosphide poisoning. *Emerg Med J* 2006; 23: e3.
7. Memiş D, *et al.* Fatal aluminium phosphide poisoning. *Eur J Anaesthesiol* 2007; 24: 292–3.
8. Shadnia S, *et al.* Unintentional poisoning by phosphine released from aluminum phosphide. *Hum Exp Toxicol* 2008; 27: 87–9.
9. Proudfoot AT. Aluminium and zinc phosphide poisoning. *Clin Toxicol* 2009; 47: 89–100.

Amitraz *(BAN, USAN, pINN)*

Amitraksi; Amitrazum; U-36059; Амитраз.

N,N'-[(Methylimino)dimethylidyne]di-2,4-xylidine.

$C_{19}H_{23}N_3$=293.4

CAS — 33089-61-1.

ATC Vet — QP53AD01.

UNII — 33IAH5017S.

Pharmacopoeias. In *BP(Vet)*. Also in *US* for veterinary use only.

BP(Vet) 2014: (Amitraz). A white to buff powder. Practically insoluble in water; decomposes slowly in alcohol; freely soluble in acetone.

Profile

Amitraz is used as a topical ectoparasiticide in veterinary practice. It is effective against various lice, mites, and ticks.

References[1–12] to poisoning with amitraz.

1. Jorens PG, *et al.* An unusual poisoning with the unusual pesticide amitraz. *Hum Exp Toxicol* 1997; 16: 600–1.
2. Aydin K, *et al.* Amitraz poisoning in children: clinical and laboratory findings of eight cases. *Hum Exp Toxicol* 1997; 16: 680–2.
3. Leung VK, *et al.* Amitraz poisoning in humans. *J Toxicol Clin Toxicol* 1999; 37: 513–14.
4. Yaramis A, *et al.* Amitraz poisoning in children. *Hum Exp Toxicol* 2000; 19: 431–3.
5. Yilmaz HL, Yildizdas DR. Amitraz poisoning, an emerging problem: epidemiology, clinical features, management, and preventive strategies. *Arch Dis Child* 2003; 88: 130–4.
6. Proudfoot AT. Poisoning with amitraz. *Toxicol Rev* 2003; 22: 71–4.
7. Gursoy S, *et al.* Intravenous amitraz poisoning. *Clin Toxicol* 2005; 43: 113–16.
8. Elinav E, *et al.* Near-fatal amitraz intoxication: the overlooked pesticide. *Basic Clin Pharmacol Toxicol* 2005; 97: 185–7.
9. Avsarogullari L, *et al.* Acute amitraz poisoning in adults: clinical features, laboratory findings, and management. *Clin Toxicol* 2006; 44: 19–23.
10. Demirel Y, *et al.* Acute amitraz intoxication: retrospective analysis of 45 cases. *Hum Exp Toxicol* 2006; 25: 613–17.
11. Caprotta CG, *et al.* Intoxicación por amitraz. *Arch Argent Pediatr* 2009; 107: 456–8.
12. Hu SY, *et al.* Torsades de pointes in amitraz poisoning. *Resuscitation* 2011; 81: 366–7.

Azamethiphos *(BAN)*

Azametifós; CGA-18809; OMS-1825; Азаметифос.

S-[(6-Chloro-2,3-dihydro-2-oxo-1,3-oxazolo[4,5-*b*]pyridin-3-yl)methyl] *O,O*-dimethyl phosphorothioate.

$C_9H_{10}ClN_2O_5PS$=324.7

CAS — 35575-96-3.

ATC Vet — QP53AF17.

UNII — 9440R8149U.

Profile

Azamethiphos is an organophosphorus insecticide (p. 2158.3) used in veterinary practice for the control of sea-lice infestation in salmon and for the control of ectoparasites in the environment.

Bendiocarb

Бендиокарб.

2,3-Isopropylidenedioxyphenyl methylcarbamate.

$C_{11}H_{13}NO_4$=223.2

CAS — 22781-23-3.

ATC Vet — QP53AE03.

UNII — QFH0ZU0A5U.

Profile

Bendiocarb is a carbamate insecticide (p. 2149.3) used in veterinary practice for the control of ectoparasites and for agricultural and household use.

Benomyl

Benomilo; Беномил.

Methyl 1-(butylcarbamoyl)benzimidazol-2-ylcarbamate.

$C_{14}H_{18}N_4O_3$=290.3

CAS — 17804-35-2.

UNII — TLW21058F5.

Profile

Benomyl is a fungicide used for the treatment and control of fungal plant diseases.

References.

1. WHO. Benomyl. *Environmental Health Criteria 148*. Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/ehc/ehc/ehc148.htm (accessed 23/04/04)
2. WHO. Benomyl health and safety guide. *IPCS Health and Safety Guide 8*. Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/hsg/hsg/hsg81_e.htm (accessed 23/04/04)

Toxicity. Although experimental evidence in *animals* has suggested a possible link between benomyl and congenital eye defects (anophthalmia) the association could not be confirmed in humans.[1-4]

1. Gilbert R. "Clusters" of anophthalmia in Britain. *BMJ* 1993; 307: 340–1.
2. Bianchi F, *et al.* Clusters of anophthalmia. *BMJ* 1994; 308: 205.
3. Kristensen P, Irgens LM. Clusters of anophthalmia. *BMJ* 1994; 308: 205–6.
4. Castilla EE. Clusters of anophthalmia. *BMJ* 1994; 308: 206.

Benzyl Benzoate

Bencilo, benzoato de; Bensylbensoat; Bentsyylibentsoaatti; Benzil Benzoat; Benzil-benzoát; Benzilbenzoatas; Benzoato de bencilo; Benzoato de Benzilo; Benzoesäurebenzylester; Benzyl Benz.; Benzylbenzoat; Benzyl-benzoát; Benzyle, benzoate de; Benzylis Benzoas; Benzylu benzoesan; Бензилбензоат.

$C_6H_5CO.OCH_2C_6H_5$=212.2.

CAS — 120-51-4.

ATC — P03AX01.

ATC Vet — QP53AX11.

UNII — N863NB338G.

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

Ph. Eur. 8: (Benzyl Benzoate). Colourless or almost colourless crystals, or a colourless or almost colourless oily liquid. F.p. is not below 17 degrees. Practically insoluble in water; miscible with alcohol, with dichloromethane, and with fatty and essential oils. Store in well-filled airtight containers. Protect from light.

USP 36: (Benzyl Benzoate). A clear, colourless, oily liquid with a slight aromatic odour. Practically insoluble in water and in glycerol; miscible with alcohol, with chloroform, and with ether. Store at a temperature not exceeding 40 degrees in well-filled airtight containers. Protect from light.

Uses and Administration

Benzyl benzoate is an acaricide used in the treatment of scabies (p. 2148.1) although other treatments are generally preferred. A 25% emulsion is applied to the whole body, usually from the neck down (although the *BNF* considers that application should be extended to the scalp, neck, face, and ears). If the application is thorough, one treatment may suffice, although the possibility of failure is lessened by a second application within 5 days. Alternatively, three applications at 12-hour intervals, without bathing, may be made, followed by bathing 12 hours after the last application. The *BNF* recommends one application to the whole body, repeated, without bathing, on the next day, and washed off 24 hours later; a third application may sometimes be necessary. Benzyl benzoate is not generally recommended for infants and children, but if used the application should be diluted to minimise the risk of irritation, although this also reduces efficacy.

Benzyl benzoate has also been used as a pediculicide.

Benzyl benzoate is also used as a solubilising agent.

Adverse Effects and Treatment

Benzyl benzoate is irritant to the eyes and mucous membranes and it may be irritant to the skin. Hypersensitivity reactions have been reported. If ingested, benzyl benzoate may cause stimulation of the CNS and convulsions. Systemic symptoms have been reported on excessive topical use. For poisoning associated with topical use the skin should be washed. Appropriate symptomatic measures should also be instituted.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Ascabiol; Benzemul; *Braz.*: Acarsan; Bencocan; Benzoax; Benzotisan; Miticocan; Parasimed; Pruridol; Sanasar; Sarnerico; Sarnilab†; Sarnodex; Scabenzil; Scabioid; Zilaben; *Ger.*: Antiscabiosum; *Gr.*: Benzogal; *Hong Kong*: Academ†; Antiscab†; Antiscabio†; Benz Application†; Wail Treatment†; *India*: Dermin; *Israel*: Scabiex; *Ital.*: Mom Lozione Preventiva; *Mex.*: Ansar†; Hastilan; *Pol.*: Novoscabin; *Port.*: Acarilbial; Piozil†; *S.Afr.*: Ascabiol; *Turk.*: Neoskabi; Scabin; *UK*: Ascabiol†; *Venez.*: Benzalcor; Benzo-Bencil; Niostal.

Multi-ingredient Preparations. *Arg.*: Anusol Duo S; Anusol-A; Bencil Scab; Detebencil; Detebencil; Hexabencil; Kinderval Max; Perbel; Permecil; Scabioderm; *Austral.*: Anusol; *Belg.*: Pulmex Baby; Pulmex†; *Braz.*: Anusol-HC; *Fr.*: Ascabiol; *Hung.*: Novascabin; *Irl.*: Anugesic-HC; Anugesic-HC; Anusol-HC; Sudocrem; *Ital.*: Antiscabbia CM; Dekar 2†; Mom Zanzara; Prurex; Skab 2†; *Malaysia*: Anucare; Anusol†; *NZ*: Anusol; *Pol.*: Cetriscabin†; *S.Afr.*: Anugesic†; *Singapore*: Anusol; Anusol; Jacutin; *Spain*: Tulgrasum Cicatrizante; *Swed.*: Tenutex; *Thai.*: Anusol†; *UK*: Anugesic-HC†; Anugesic-HC; Anusol-HC, Plus HC; Sudocrem; *Ukr.*: Sudocrem (Судокрем); *USA*: Anumed HC; Anumed; Hemril; *Venez.*: Kertyol.

Pharmacopoeial Preparations
BP 2014: Benzyl Benzoate Application;
USP 36: Benzyl Benzoate Lotion.

Bioallethrin *(BAN)*

Allethrin I; Bioaletrina; Depallethrin; Биоаллетрин.

(*RS*)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

$C_{19}H_{26}O_3$=302.4.

CAS — 584-79-2.

ATC — P03AC02.

ATC Vet — QP53AC02.

UNII — G79DM7O471.

Profile

Bioallethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1). It is used topically, with the synergist piperonyl butoxide (p. 2160.2), in the treatment of pediculosis (p. 2147.3). It is also used in anti-mosquito devices and for the control of household insect pests.

References.

1. WHO. Allethrins. *Environmental Health Criteria 87*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc87.htm (accessed 23/04/04)
2. WHO. Allethrins health and safety guide. *IPCS Health and Safety Guide 24*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg024.htm (accessed 23/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Cinq sur Cinq; Moustico-logne†; *UK*: Actomite.

Multi-ingredient Preparations. *Arg.*: Limpacid; Para Piojicida; Scabioderm; *Austral.*: Paralice; *Belg.*: Para; *Fr.*: Para Special Poux; *Ger.*: Jacutin; Spregal†; *Israel*: Monocide†; *Ital.*: Cruzzy; *Neth.*: Para-Speciaal†.

Brodifacoum

Brodifacum; WBA-8119; Бродифакум.

3-[3-(4′-Bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin.

$C_{31}H_{23}BrO_3$=523.4.

CAS — 56073-10-0.

UNII — A25P3CP5S7.

NOTE. The name "superwarfarin" has been used to describe several anticoagulant rodenticides, including brodifacoum, bromadiolone (below), chlorophacinone (p. 2150.3), and difenacoum (p. 2153.2).

Profile

Brodifacoum is an anticoagulant rodenticide. It is reported to be effective in warfarin-resistant strains of rodents.

References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 23/04/04)
2. WHO. Brodifacoum health and safety guide. *IPCS Health and Safety Guide 93*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg093.htm (accessed 23/04/04)

Toxicity. Brodifacoum, a second-generation anticoagulant rodenticide, inhibits prothrombin synthesis to cause bleeding that may be occult.[1] It is absorbed from the gastrointestinal tract; dermal absorption is possible. Poisons containing 100 mg in each kg of bait are not hazardous to man; more concentrated forms are particularly hazardous and their availability should be restricted. Baits, which should be prepared only by trained personnel, should contain a suitable marker-dye.

There have been reports of poisoning with brodifacoum.[2-10]

1. WHO. Safe use of pesticides: ninth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 720* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_720.pdf (accessed 21/07/08)
2. Watts RG, *et al.* Accidental poisoning with a superwarfarin compound (brodifacoum) in a child. *Pediatrics* 1990; 86: 883–7.
3. Ross GS, *et al.* An acquired hemorrhagic disorder from long-acting rodenticide ingestion. *Arch Intern Med* 1992; 152: 410–12.
4. Kruse JA, Carlson RW. Fatal rodenticide poisoning with brodifacoum. *Ann Emerg Med* 1992; 21: 331–6.
5. Tecimer C, Yam LT. Surreptitious superwarfarin poisoning with brodifacoum. *South Med J* 1997; 90: 1053–5.
6. Corke PJ. Superwarfarin (brodifacoum) poisoning. *Anaesth Intensive Care* 1997; 25: 707–9.
7. La Rosa FG, *et al.* Brodifacoum intoxication with marijuana smoking. *Arch Pathol Lab Med* 1997; 121: 67–9.
8. Miller MA, *et al.* Rapid identification of surreptitious brodifacoum poisoning by analysis of vitamin K-dependent factor activity. *Am J Emerg Med* 2006; 24: 383.
9. Olmos V, López CM. Brodifacoum poisoning with toxicokinetic data. *Clin Toxicol* 2007; 45: 487–9.
10. Kapadia P, Bona R. Acquired deficiency of vitamin K-dependent clotting factors due to brodifacoum ingestion. *Conn Med* 2008; 72: 207–9.

Bromadiolone

Bromadiolona; Бромадиолон.

3-[3-(4′-Bromobiphenyl-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxycoumarin.

$C_{30}H_{23}BrO_4$=527.4.

CAS — 28772-56-7.

NOTE. The name "superwarfarin" has been used to describe several anticoagulant rodenticides including brodifacoum (above), bromadiolone, chlorophacinone (p. 2150.3), and difenacoum (p. 2153.2).

Profile

Bromadiolone is an anticoagulant rodenticide.

References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 23/04/04)
2. WHO. Bromadiolone health and safety guide. *IPCS Health and Safety Guide 94*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg094.htm (accessed 23/04/04)

Toxicity. Bromadiolone, a second-generation anticoagulant rodenticide, inhibits prothrombin synthesis to cause bleeding that may be occult.[1] It is absorbed from the gastrointestinal tract; dermal absorption is possible. Poisons containing 100 mg in each kg of bait are not hazardous to man; more concentrated forms are particularly hazardous and their availability should be restricted. Baits, which should be prepared only by trained personnel, should contain a suitable marker-dye.

There have been reports of poisoning with bromadiolone.[2-5]

1. WHO. Safe use of pesticides: ninth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 720* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_720.pdf (accessed 21/07/08)
2. Greeff MC, *et al.* "Superwarfarin" (bromodialone) poisoning in two children resulting in prolonged anticoagulation. *Lancet* 1987; ii: 1269.
3. Chow EY, *et al.* A case of bromadiolone (superwarfarin) ingestion. *CMAJ* 1992; 147: 60–2.
4. Grobosch T, *et al.* Acute bromadiolone intoxication. *J Anal Toxicol* 2006; 30: 281–6.
5. Lo VM, *et al.* Bromadiolone toxicokinetics: diagnosis and treatment implications. *Clin Toxicol* 2008; 1–8.

Bromophos

Bromofos; Bromofós; OMS-658; Бромофос.

O-4-Bromo-2,5-dichlorophenyl *O*,*O*-dimethyl phosphorothioate.

$C_8H_8BrCl_2O_3PS$=366.0.

CAS — 2104-96-3.

ATC Vet — QP53AF11.

Profile

Bromophos is an organophosphorus insecticide (p. 2158.3) used in veterinary practice for the control of ectoparasites in the environment. It has also been used as an agricultural insecticide.

Butopyronoxyl

Butopiroxinilo; Indalona; Indalone; Бутопироноксил.

Butyl 3,4-dihydro-2,2-dimethyl-4-oxo-2*H*-pyran-6-carboxylate.

$C_{12}H_{18}O_4$=226.3.

CAS — 532-34-3.

UNII — 415PG5VZ0V.

Profile

Butopyronoxyl has been used as an insect repellent.

Carbamate Insecticides

Insecticidas del grupo de los carbamatos.

Description. The carbamate insecticides are *N*-substituted esters of carbamic acid.

References.

1. WHO. Carbamate pesticides: a general introduction. *Environmental Health Criteria 64*. Geneva: WHO,1986. Available at: http://www.inchem.org/documents/ehc/ehc/ehc64.htm (accessed 24/07/08)

Adverse Effects

As for Organophosphorus Insecticides, p. 2158.3.

The carbamates are cholinesterase inhibitors, differing from the organophosphorus insecticides in that the inhibition they produce is generally less intense and more rapidly reversible. In addition, they do not appear to enter the CNS as readily and severe central effects are therefore uncommon.

Treatment of Adverse Effects

If substantial amounts of carbamate insecticides have been ingested the use of gastric lavage should be considered if the patient presents within 1 hour. Contaminated clothing should be removed and the skin washed with soap and water. Treatment is largely symptomatic and supportive and includes atropine for muscarine effects, although this may not always be necessary due to the rapidly reversible nature of the cholinesterase inhibition produced. The use of pralidoxime is controversial, see Carbamate Poisoning, under Pralidoxime, p. 1571.3.

References.
1. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 21/07/08)
2. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners.* 2nd ed. London: DoH, The Stationery Office, 1996.
3. Rosman Y, *et al.* Carbamate poisoning: treatment recommendations in the setting of a mass casualties event. *Am J Emerg Med* 2009; 27: 1117–24.

Carbaryl *(BAN)*

Caprolin; Carbatil (pINN); Carbarilo; Carbarilum; Karbaril; OMS-29; Карбарил.

1-Naphthyl methylcarbamate.

$C_{12}H_{11}NO_2$=201.2

CAS — 63-25-2.

ATC Vet — QP53AE01.

UNII — R890C8J3N1.

Pharmacopoeias. In *Br.*

BP 2014: (Carbaryl). A white to off-white or light grey powder which darkens on exposure to light. Very slightly soluble in water; soluble in alcohol and in acetone. Store at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Carbaryl is a carbamate insecticide (p. 2149.3). It is used as a 0.5 or 1.0% lotion or shampoo in the treatment of head and pubic pediculosis (p. 2147.3). Lotions are generally preferred to shampoos as the contact time is longer. Aqueous lotions are preferred to treat pubic lice because alcoholic lotions are irritant to excoriated skin and the genitalia; aqueous lotions may also be preferable in asthmatic subjects or children to avoid alcoholic fumes. Skin or hair treated with an alcohol-based preparation should be allowed to dry naturally.

Carbaryl is also used as a topical ectoparasiticide in veterinary practice and as an agricultural, horticultural, and household insecticide.

References.
1. WHO. Carbaryl health and safety guide. *IPCS Health and Safety Guide 78.* Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/hsg/hsg/hsg78_e.htm (accessed 23/04/04)
2. WHO. Carbaryl. *Environmental Health Criteria 153.* Geneva: WHO, 1994. Available at: http://www.inchem.org/documents/ehc/ehc/ehc153.htm (accessed 23/04/04)

Adverse Effects and Treatment

As for Carbamate Insecticides, p. 2149.3. Carbaryl may be absorbed after ingestion, inhalation, or skin contamination.

Carbaryl has been reported to produce neoplasms in *mice* and *rats* and in late 1995 the UK DoH advised that it would be prudent to consider carbaryl as a potential human carcinogen; its medicinal use was limited to prescription only. However, the DoH emphasised that the risk was a theoretical one and that any risk from the intermittent use of head lice preparations was likely to be very small.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.:* Lysatox; *Irl.:* Suleo-C†; *Israel:* Hafit; *UK:* Carylderm.

Pharmacopoeial Preparations
BP 2014: Carbaryl Lotion.

Carbosulfan

Carbosulfan; Карбосульфан.

2,3-Dihydro-2,2-dimethylbenzofuran-7-yl (dibutylaminothio) methylcarbamate.

$C_{20}H_{32}N_2O_3S$=380.5

CAS — 55285-14-8.

UNII — V1DGN4AK6G.

Profile

Carbosulfan is a carbamate insecticide (p. 2149.3) used in agriculture and for the larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2).

Chloralose *(rINN)*

Alphachloralose; Chloralosane; α-Chloralose; Chloralosum; Cloralosa; α-Cloralosa; Glucochloral; Xnopanosa.

(*R*)-1,2-*O*-(2,2,2-Trichloroethylidene)-α-D-glucofuranose.

$C_8H_{11}Cl_3O_6$=309.5

CAS — 15879-93-3.

UNII — 2388Z29MUE.

Profile

Chloralose has general properties similar to those of cloral hydrate (p. 1055.2), of which it is a derivative. It is used as a rodenticide. It was formerly used for its hypnotic properties.

Chlordane

Chlordan; Clordán; Clordano; Хлордан.

1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene.

$C_{10}H_6Cl_8$=409.8

CAS — 57-74-9.

UNII — A9RLM212CY.

Profile

Chlordane is a chlorinated insecticide (below). Its use is limited, or even prohibited, in some countries because of toxicity due to its persistent nature.

References.
1. Kutz FW, *et al.* A fatal chlordane poisoning. *J Toxicol Clin Toxicol* 1983; 20: 167–74.
2. Olanoff LS, *et al.* Acute chlordane intoxication. *J Toxicol Clin Toxicol* 1983; 20: 291–306.
3. WHO. Chlordane. *Environmental Health Criteria 34.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc34.htm (accessed 23/04/04)
4. WHO. Chlordane health and safety guide. *IPCS Health and Safety Guide 13.* Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg013.htm (accessed 23/04/04)

Chlorinated Insecticides

Insecticidas clorados.

Uses

The chlorinated or organochlorine insecticides were widely used but, because of persistence in man, many have been banned or restricted.

References.
1. WHO. Polychlorinated biphenyls and terphenyls. *Environmental Health Criteria 140.* Geneva: WHO,1993. Available at: http://www.inchem.org/documents/ehc/ehc/ehc140.htm (accessed 28/05/04)
2. WHO. Polychlorinated biphenyls (PCBs) and polychlorinated terphenyls (PCTs) health and safety guide. *IPCS Health and Safety Guide 68.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/hsg/hsg/hsg68.htm (accessed 28/05/04)

Adverse Effects

Chlorinated or organochlorine insecticides form a very wide group and the toxicity of individual members varies considerably. In general these insecticides produce symptoms consistent with CNS stimulation. They may be absorbed through the respiratory and gastrointestinal tracts and through the skin.

Symptoms of acute poisoning include nausea and vomiting, paraesthesia, giddiness, tremors, convulsions, coma, and respiratory failure. Liver, kidney, and myocardial toxicity have been reported. Effects on the blood include agranulocytosis and aplastic anaemia. Symptoms may be complicated by the effects of the solvent.

Chlorinated insecticides have been reported to enhance microsomal hepatic enzyme activity. Skin reactions can occur after contact.

Polychlorinated biphenyl (PCB) and terphenyl compounds were formerly used as insecticides in many countries. They accumulate in body fat and are not readily excreted, although they are distributed into breast milk and possibly cross the placenta; because of this and because of accidental contamination they remain a cause for concern. The related polybrominated biphenyl compounds (PBB), which have no insecticidal uses, have also been absorbed by humans after accidental contamination of the food chain.

Some chlorinated insecticides have weak oestrogenic effects; it has been proposed that exposure may increase the risk of breast cancer.

Treatment of Adverse Effects

If chlorinated insecticides have been ingested, gastric lavage or activated charcoal may be considered if the patient presents within 1 hour. Contaminated clothing should be removed and the skin washed with soap and water. Treatment is largely symptomatic and supportive with treatment of CNS stimulation such as hyperactivity and convulsions.

References.
1. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 24/07/08)
2. Proudfoot A, ed. Pesticide poisoning: notes for the guidance of medical practitioners. 2nd ed. London: DoH, The Stationery Office, 1996.

Chlorophacinone

Clorofacinona; LM-91; Хлорфацинон.

2-[2-(4-Chlorophenyl)-2-phenylacetyl]indane-1,3-dione.

$C_{23}H_{15}ClO_3$=374.8

CAS — 3691-35-8.

UNII — 34Y6E0063Y.

NOTE. The name "superwarfarin" has been used to describe several anticoagulant rodenticides, including brodifacoum (p. 2149.2), bromadiolone, (p. 2149.3) chlorophacinone and difenacoum (p. 2153.2).

Profile

Chlorophacinone is an indanedione derivative used as an anticoagulant rodenticide. It is also reported to uncouple oxidative phosphorylation with consequent stimulation of cellular metabolism which may contribute to its toxicity.

References.
1. Burucoa C, *et al.* Chlorophacinone intoxication: biological and toxicological study. *J Toxicol Clin Toxicol* 1989; 27: 79–89.
2. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 17.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 28/05/04)
3. Lagrange F, *et al.* Toxicological management of chlorophacinone poisoning. *Acta Clin Belg Suppl* 1999; 1: 13–16.
4. Papin F, *et al.* Lethal paradoxical cerebral vein thrombosis due to suspicious anticoagulant rodenticide intoxication with chlorophacinone. *Forensic Sci Int* 2007; 166: 85–90.

Chloropicrin

Cloropicrina; Nitrochloroform; Nitrocloroformo; Nitrotriclorometano; Хлорпикрин.

Trichloronitromethane.

CCl_3NO_2=164.4

CAS — 76-06-2.

UNII — 14JTX7Z7U2.

Profile

Chloropicrin is a lachrymatory agent with an intense odour. It is intensely irritating to the skin and mucous membranes. It is an insecticide and is used for fumigating stored grain and soil. Chloropicrin is also added to other fumigants as a warning gas.

Chlorpyrifos *(BAN)*

Clorpirifós; Хлорпирифос.

O,O-Diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate.

$C_9H_{11}Cl_3NO_3PS$=350.6

CAS — 2921-88-2.

UNII — JCS581644W.

Profile

Chlorpyrifos is an organophosphorus insecticide (p. 2158.3) used in agriculture.

Cycloheximide *(rINN)*

Cicloheximida; Cycloheximidum; Cycloheximide (USAN); Cycloheximide; U-4527; Циклогексимид.

3-[(2*R*)-2-[(1*S*,3*S*,5*S*)-3,5-Dimethyl-2-oxocyclohexyl]-2-hydroxyethyl]glutarimide.

$C_{15}H_{23}NO_4$=281.4

CAS — 66-81-9.

UNII — 98600C0908.

Profile

Cycloheximide is an antimicrobial substance produced by strains of *Streptomyces griseus.* It has antifungal properties and has been used for the treatment and control of certain mycotic plant diseases.

Clofenotane (rINN)

Chlorofenotano; Chlorophenothane; Chlorphenothanum; Clofénotane; Clofenotano; Clofenotanum; Clorofenotano; DDT; Dichlorodiphenyltrichloroethane; Dichophanum; Dicophane; Klofenotaani; Klofenotan; Клофенотан.

1,1,1-Trichloro-2,2-bis(4-chlorophenyl)ethane.

$C_{14}H_9Cl_5$=354.5

CAS — 50-29-3.

ATC — P03AB01.

ATC Vet — QP53AB01.

UNII — CIW5S16655.

Pharmacopoeias. In *It.*

Uses

Clofenotane is a chlorinated insecticide (p. 2150.2). It is a stomach and contact poison and retains its activity for long periods under a variety of conditions. It is effective against disease vectors such as fleas, lice, and mosquitoes and has been applied topically for pediculosis (p. 2147.3) and scabies (p. 2148.1), although more suitable alternatives exist.

Because of the extreme persistence of clofenotane, concern over its effect in the environment, and the problem of resistance, the widespread use of clofenotane is now generally discouraged. It is no longer used in some countries while in others its use is limited.

Despite reservations regarding the use of clofenotane for vector control, many countries have relied on it for the control of both malaria and visceral leishmaniasis. WHO has concluded[1,2] that clofenotane might be used provided:

- that it was used only for indoor spraying
- that it was known to be effective
- that it was manufactured to WHO's specifications
- that the necessary safety precautions were taken in its use and disposal

However, they recommended further investigation of the effects of clofenotane in breast milk and of suspected carcinogenicity, as well as clarification of the significance of the reduced density of muscarinic receptors caused by clofenotane.

1. WHO. WHO expert committee on malaria: twentieth report. *WHO Tech Rep Ser 892* 2000. Available at: http://libdoc.who.int/trs/WHO_TRS_892.pdf (accessed 21/07/08)
2. WHO Global Malaria Programme. Indoor residual spraying: use of indoor residual spraying for scaling up global malaria control and elimination 2006. Available at: http://malaria.who.int/docs/IRSposition.pdf (accessed 21/04/08)

Adverse Effects and Treatment

As for Chlorinated Insecticides, p. 2150.2.

References.

1. WHO. DDT and its derivatives. *Environmental Health Criteria 9*. Geneva: WHO, 1979. Available at: http://www.inchem.org/documents/ehc/ehc/ehc009.htm (accessed 28/05/04)
2. WHO. DDT and its derivatives—environmental aspects. *Environmental Health Criteria 83*. Geneva: WHO,1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc83.htm (accessed 28/05/04)

Carcinogenicity. Some small epidemiological studies have suggested that certain organochlorines, namely 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), a metabolite of clofenotane, and polychlorinated biphenyls (PCBs), might increase the risk of breast cancer in women. However, re-analysis[1,2] of the available data indicated that an association with breast cancer was unlikely for clofenotane; there was no evidence for an association with the PCBs. Any link between exposure to clofenotane and the development of testicular cancer in men was also refuted[3] after long-term monitoring of populations in Scandinavia.

1. Key T, Reeves G. Organochlorines in the environment and breast cancer. *BMJ* 1994; 308: 1520–1.
2. van't Veer P, *et al.* DDT (dicophane) and postmenopausal breast cancer in Europe: case-control study. *BMJ* 1997; 315: 81–5.
3. Ekbom A, *et al.* DDT and testicular cancer. *Lancet* 1996; 347: 553–4.

Effects on fertility. A metabolite of clofenotane, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), was reported[1] to have anti-androgenic properties in *rats* and exposure to clofenotane might account for a previously reported decline in male fertility and an increase in male reproductive abnormalities.

1. Kelce WR, *et al.* Persistent DDT metabolite p,p'-DDE is a potent androgen receptor antagonist. *Nature* 1995; 375: 581–5.

Effects on the nervous system. A retrospective study[1] found that retired malaria workers exposed long-term to clofenotane did less well in neurobehavioural tests than a control group, and had an increase in neuropsychological and psychiatric symptoms.

1. van Wendel de Joode B, *et al.* Chronic nervous-system effects of long-term occupational exposure to DDT. *Lancet* 2001; 357: 1014–16.

Pregnancy. In a large prospective study[1] of children born between 1959 and 1966, an association was found between preterm births and small-for-gestational-age babies, and maternal concentrations of a metabolite of clofenotane, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) measured in serum samples which had been stored during pregnancy.

1. Longnecker MP, *et al.* Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. *Lancet* 2001; 358: 110–14.

Pharmacokinetics

Clofenotane may be absorbed after ingestion or inhalation or through the skin. Clofenotane is stored in the body, particularly in body fat, and is very slowly eliminated. It crosses the placenta and appears in breast milk. It is metabolised in the body to the ethylene derivative, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE); the acetic acid derivative (DDA) also appears in the urine.

Clofenvinfos (BAN, rINN)

Chlorfenvinphos; Chlorofenwinfos; Clofenvinfós; Clofenvinfosum; Клофенвинфос.

2-Chloro-1-(2,4-dichlorophenyl)vinyl diethyl phosphate.

$C_{12}H_{14}Cl_3O_4P$=359.6

CAS — 470-90-6.

UNII — F2G9X51W91.

Profile

Clofenvinfos is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice and in agriculture.

Copper Naphthenate

Cobre, naftenato de; Нафтенат Меди.

CAS — 1338-02-9.

Profile

Copper naphthenate is the copper salt of naphthenic acid and is classified as a general use pesticide. It is used to preserve wood against a broad spectrum of fungi, termites, and other wood-destroying insects. Copper naphthenate has also been used as a topical antifungal in veterinary medicine.

Copper Oleate

Cobre, oleato de; Oléate de Cuivre; Олеат Меди.

$Cu(C_{18}H_{33}O_2)_2$=626.5

CAS — 1120-44-1.

UNII — KT1O45G674.

Profile

Copper oleate has been used topically as an insecticide for the treatment of pediculosis (p. 2147.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Plus & Plus.

Coumafos (BAN, rINN)

Bayer-21199; Coumafosum; Coumaphos; Cumafós; Kumafoosi; Kumafos; Кумафос.

O-3-Chloro-4-methyl-7-coumarinyl *O,O*-diethyl phosphorothioate.

$C_{14}H_{16}ClO_5PS$=362.8

CAS — 56-72-4.

ATC Vet — QP53AF08.

UNII — L08SZ5Z5JC.

Profile

Coumafos is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice.

Coumatetralyl

Cumatetralilo; Кумателралил.

4-Hydroxy-3-(1,2,3,4-tetrahydro-1-naphthyl)coumarin.

$C_{19}H_{16}O_3$=292.3

CAS — 5836-29-3.

Profile

Coumatetralyl is an anticoagulant rodenticide.

References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 28/05/04)

Cyfluthrin (BAN)

Bay-VI-1704; Ciflutrina; Cyfluthin; Цифлутрин.

(*RS*)-α-Cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.

$C_{22}H_{18}Cl_2FNO_3$=434.3

CAS — 68359-37-5.

ATC — P03BA01.

ATC Vet — QP53AC12.

UNII — SCM2QLZ6S0.

Profile

Cyfluthrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in agriculture and veterinary practice, and in the vector control of malaria (p. 644.1).

Preparations

Proprietary Preparations (details are given in Volume B)

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

Cyhalothrin (BAN)

Cihalotrina; Cyhalotryna; PP-563; Цигалотрин.

(*RS*)-α-Cyano-3-phenoxybenzyl (*Z*)-(1*RS*,3*RS*)-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate.

$C_{23}H_{19}ClF_3NO_3$=449.9

CAS — 68085-85-8.

ATC Vet — QP53AC06.

UNII — V0V73PEB8M.

Profile

Cyhalothrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) that is used, particularly as a mixture of the (*Z*)-(1*R*,3*R*) *S* ester and the (*Z*)-(1*S*,3*S*) *R* ester (known as lambda-cyhalothrin), for the control of insect pests in public health. It has also been used in agriculture and in veterinary practice.

References.

1. WHO. Cyhalothrin. *Environmental Health Criteria 99*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc99.htm (accessed 23/04/04)
2. WHO. Cyhalothrin and lambda-cyhalothrin health and safety guide. *IPCS Health and Safety Guide 38*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/hsg/hsg/hsg038.htm (accessed 23/04/04)

Cymiazole

CGA-50439; CGA-192357 (cymiazole hydrochloride); Cimiazol; Cymiazol; Cymiazolum; Symiatsoli; Xymiazole; Цимиазол.

2,4-Dimethyl-*N*-(3-methyl-2(3*H*)-thiazolylidene)benzenamine.

$C_{12}H_{14}N_2S$=218.3

CAS — 61676-87-7 (cymiazole); 121034-85-3 (cymiazole hydrochloride).

ATC Vet — QP53AA02.

UNII — 7XR6MQQ68K.

Profile

Cymiazole is a pesticide used in beekeeping.

Cypermethrin (BAN)

Cipermetrina; Cypermetryna; NRDC-149; Циперметрин.

(*RS*)-α-Cyano-3-phenoxybenzyl (1*RS*,3*RS*)-(1*RS*,3*RS*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.

$C_{22}H_{19}Cl_2NO_3$=416.3

CAS — 52315-07-8.

ATC — P03BA02.

ATC Vet — QP53AC08.

UNII — 1TR49121NP.

Alpha-cypermethrin (BAN)

Alfacipermetrina; Альфа-циперметрин.

(*SR*)-α-Cyano-3-phenoxybenzyl (1*RS*,3*RS*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.

$C_{22}H_{19}Cl_2NO_3$=416.3

CAS — 67375-30-8.

UNII — 99W8X078CA.

Profile

Cypermethrin, an isomeric mixture containing alpha-cypermethrin, is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in veterinary practice as a topical ectoparasiticide and to control sea-lice infestation in salmon. It is also used in agriculture. Zeta-cypermethrin is also used. Alpha-cypermethrin is used in agriculture and for vector control in the management of malaria (p. 644.1).

References.
1. WHO. Cypermethrin. *Environmental Health Criteria 82*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc82.htm (accessed 23/04/04)
2. WHO. Cypermethrin health and safety guide. *IPCS Health and Safety Guide 22*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg022.htm (accessed 23/04/04)
3. WHO. Alpha-cypermethrin. *Environmental Health Criteria 142*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc142.htm (accessed 23/04/04)

Cyromazine *(BAN, rINN)*

CGA-72662; Ciromazina; Cyromazinum; Циромазин.
N-Cyclopropyl-1,3,5-triazine-2,4,6-triamine.
$C_6H_{10}N_6$=166.2
CAS — 66215-27-8.
UNII — CA49Y29RA9.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Cyromazine). A white or off-white, odourless, crystalline powder. Slightly soluble in water and in methyl alcohol.

Profile

Cyromazine is used as a topical ectoparasiticide in veterinary practice.

Cythioate *(BAN)*

Citioato; Цитиоат.
O,O-Dimethyl *O*-(4-sulphamoylphenyl) phosphorothioate.
$C_8H_{12}NO_5PS_2$=297.3
CAS — 115-93-5.
ATC Vet — QP53AF10; QP53BB01.
UNII — 3OOH7Q4333.

Profile

Cythioate is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is given orally to the host animal.

Daminozide

Daminozida; Даминозид.
N-Dimethylaminosuccinamic acid.
$C_6H_{12}N_2O_3$=160.2
CAS — 1596-84-5.

Profile

Daminozide is a plant growth regulator that has been used in pesticides to improve fruit crops. There have been concerns about residues of the chemical in the fruit.

Deltamethrin *(BAN)*

Decamethrin; Decametrina; Deltamethrinum; Deltametriini; Deltametrin; Deltametrina; Deltametryna; NRDC-161; Дельтаметрин.
(*S*)-α-Cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{22}H_{19}Br_2NO_3$=505.2
CAS — 52918-63-5.
ATC — P03BA02.
ATC Vet — QP53AC11.
UNII — 2JT58R821G.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Deltamethrin). A white to buff-coloured crystalline powder. Insoluble in water; soluble in alcohol and in acetone.

Profile

Deltamethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in the vector control of malaria (p. 644.1). It is also used as a topical ectoparasiticide in veterinary practice and as an agricultural and household insecticide.

References.
1. WHO. Deltamethrin health and safety guide. *IPCS Health and Safety Guide 30*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg030.htm (accessed 26/04/04)
2. WHO. Deltamethrin. *Environmental Health Criteria 97*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc97.htm (accessed 26/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Deltacid; Deltalab; Deltapil; Deotrin; Pediderm; *Fr.*: Cinq sur Cinq; Pharmavoyage Moustiquaires; *Venez.*: Nopucid.

Multi-ingredient Preparations. *Arg.*: Deca-Scab; Hexa-Defital NF; Nopucid Compuesto; Nopucid Rapida; *Braz.*: Deltacid Plus; *Chile*: Launol.

Dibromochloropropane

DBCP; Dibromodoropropano; Дибромохлоропропан.
1,2-Dibromo-3-chloropropane.
$C_3H_5Br_2Cl$=236.3
CAS — 96-12-8.
UNII — 96K0FD4803.

Profile

Dibromochloropropane has been used as a pesticide. Low sperm counts and evidence of testicular damage have occurred in workers exposed to dibromochloropropane.

Dibutyl Phthalate

Butyl Phthalate; DBP; Dibutil-ftalát; Dibutilo ftalatas; Dibutilo, ftalato de; Dibutyle, phtalate de; Dibutylftalat; Dibutyl-ftalát; Dibutylis Phthalas; Dibutylphthalat; Dibutylu ftalan; Dibutyyliftalaatti; Дибутилфталат.
Dibutyl benzene-1,2-dicarboxylate.
$C_{16}H_{22}O_4$=278.3
CAS — 84-74-2.
ATC — P03BX03.
UNII — 2286E5R2KE.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Dibutyl Phthalate). A clear, oily, colourless or *very slightly yellow liquid. Practically insoluble in water;* miscible with alcohol. Store in airtight containers.

USNF 31: (Dibutyl Phthalate). A clear, oily, colourless or very slightly yellow liquid. Practically insoluble in water; miscible with alcohol and with ether. Store in airtight containers.

Uses and Administration

Dibutyl phthalate has been used as an insect repellent although it is slightly less effective than dimethyl phthalate (p. 2153.3). It is less volatile and less easily removed by washing than dimethyl phthalate, and its chief use therefore has been for the impregnation of clothing.

Dibutyl phthalate has also been used in latex adhesives, as a solvent in dyes, in coatings of medications, in cosmetics, and as a plasticiser.

References.
1. WHO. Di-n-butyl phthalate. *Environmental Health Criteria 189*. Geneva: WHO. 1997. Available at: http://www.inchem.org/documents/ehc/ehc/ehc189.htm (accessed 26/04/04)
2. Kamrin MA. Phthalate risks, phthalate regulation, and public health: a review. *J Toxicol Environ Health B* 2009; 12: 157–74.

Adverse Effects and Precautions

Dibutyl phthalate has occasionally caused hypersensitivity reactions. As with other phthalates contact with plastics should be avoided.

Dichlorophenoxyacetic Acid

2,4-D; Diclorofenoxiacético, ácido; Дихлорфеноксиуксусная кислота.
2,4-Dichlorophenoxyacetic acid.
$C_8H_6Cl_2O_3$=221.0
CAS — 94-75-7.
UNII — 2577AQ9262.

Uses

Dichlorophenoxyacetic acid is a herbicide widely used for weed control in cereals and other crops. It is usually used as its salts or esters with other herbicides.

Adverse Effects, Treatment, and Precautions

Most cases of poisoning with dichlorophenoxyacetic acid have involved its ingestion with other herbicides; the solvent may also play a part in any toxicity. There is little pattern to the range of adverse effects that may occur after ingestion, inhalation, or topical exposure.

Adverse effects have involved the CNS and peripheral nervous system, muscles, and the cardiovascular system. Gastrointestinal effects are common with poisoning. Hepatotoxicity, nephrotoxicity, and pulmonary disorders have occurred but it is not clear that dichlorophenoxyacetic acid contributed to the toxicity. The role of phenoxyacetic acids in cancer is discussed under trichlorophenoxyacetic acid (p. 2162.3).

Activated charcoal or possibly gastric lavage should be considered after ingestion of substantial amounts if the patient presents within 1 hour. Contaminated clothing should be removed and the skin washed with soap and water. Forced alkaline diuresis or haemodialysis have been reported to be effective in removing dichlorophenoxyacetic acid; the latter is considered more effective. Further treatment is symptomatic.

References.
1. WHO. 2,4-Dichlorophenoxyacetic acid (2,4-D). *Environmental Health Criteria 29*. Geneva: WHO,1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc29.htm (accessed 26/04/04)
2. WHO. 2,4-Dichlorophenoxyacetic (2,4-D) health and safety guide. *IPCS Health and Safety Guide 5*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg005.htm (accessed 26/04/04)
3. WHO. 2,4-Dichlorophenoxyacetic acid (2,4-D)—environmental aspects. *Environmental Health Criteria 84*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc84.htm (accessed 26/04/04)
4. Bradberry SM, *et al.* Mechanisms of toxicology, clinical features, and management of acute chlorophenoxy herbicide poisoning: a review. *J Toxicol Clin Toxicol* 2000; 38: 111–22.
5. Garabrant DH, Philbert MA. Review of 2,4-dichlorophenoxyacetic acid (2,4-D) epidemiology and toxicology. *Crit Rev Toxicol* 2002; 32: 233–57.
6. Bradberry SM, *et al.* Poisoning due to chlorophenoxy herbicides. *Toxicol Rev* 2004; 23: 65–73.

Dichlorvos *(BAN, USAN, rINN)*

DDVP; Dichlorfos; Diclorvosum; Diclorvós; NSC-6738; OMS-14; SD-1750; Дихлорвос.
2,2-Dichlorovinyl dimethyl phosphate.
$C_4H_7Cl_2O_4P$=221.0
CAS — 62-73-7.
ATC Vet — QP52AB03; QP53AF04.
UNII — 7U370BPS14.

Pharmacopoeias. In *Fr.* for veterinary use.

Profile

Dichlorvos is an organophosphorus insecticide (p. 2158.3) of short persistence, effective against a wide range of insects. It is sometimes used as a fumigant. It has been used for the extermination of insects in aircraft (disinsection). It is also used as a topical ectoparasiticide and as an anthelmintic in veterinary practice. Concern has been expressed over its possible carcinogenicity.

References.
1. WHO. Dichlorvos health and safety guide. *IPCS Health and Safety Guide 18*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg018.htm (accessed 26/04/04)
2. WHO. Dichlorvos. *Environmental Health Criteria 79*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/ehc/ehc/ehc79.htm (accessed 26/04/04)
3. Van Maele-Fabry G, *et al.* Dichlorvos and carcinogenicity: a systematic approach to a regulatory decision. *Regul Toxicol Pharmacol* 2000; 31: 1–21.
4. Ishmael J, *et al.* Dichlorvos—a comprehensive review of 11 rodent carcinogenicity studies. *Regul Toxicol Pharmacol* 2006; 44: 238–48.
5. Booth ED, *et al.* Review of the in vitro and in vivo genotoxicity of dichlorvos. *Regul Toxicol Pharmacol* 2007; 49: 316–26.

Dieldrin *(BAN, pINN)*

Dieldrina; Dieldrine; Dieldrinum; Dieldryna; Диалдрин.
CAS — 60-57-1 (HEOD).
UNII — I0246D2ZS0.

Description. Dieldrin contains about 85% of (1*R*,4*S*,5*S*,8*R*)-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4:5,8-dimethanonaphthalene (HEOD), $C_{12}H_8Cl_6O$ = 380.9. The remaining 15% is mainly chlorinated organic compounds related to HEOD.

Uses

Dieldrin is a chlorinated insecticide (p. 2150.2) formerly used as a sheepdip. Its use is now limited to a few specified purposes such as termite control.

Adverse Effects and Treatment

As for Chlorinated Insecticides, p. 2150.2.

Dieldrin is more toxic than clofenotane (p. 2151.1) and is readily absorbed through the skin.

References.
1. WHO. Aldrin and dieldrin. *Environmental Health Criteria 91*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc91.htm (accessed 26/04/04)

2. WHO. Aldrin and dieldrin health and safety guide. *IPCS Health and Safety Guide 21*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg021.htm (accessed 26/04/04)
3. Høyer AP, *et al.* Organochlorine exposure and risk of breast cancer. *Lancet* 1998; 352: 1816–20.
4. Jorgenson JL. Aldrin and dieldrin: a review of research on their production, environmental deposition and fate, bioaccumulation, toxicology, and epidemiology in the United States. *Environ Health Perspect* 2001; 109 (suppl 1): 113–39.

Di-(2-ethylhexyl)adipate

DEHA; Dioctilo, adipato de; Dioctyl Adipate; DOA; Диоктиладипинат.
$C_{22}H_{42}O_4$=370.6
CAS — 103-23-1.
UNII — MBY1SL921L

NOTE. Do not confuse with the plasticiser di-*n*-octyl adipate (*CAS*—123-79-5), which is also referred to as dioctyl adipate.

Profile

Di-(2-ethylhexyl)adipate is used as an insect repellent. It is also used as a plasticiser by the plastics industry; concern about the migration of this and other plasticisers into foodstuffs from polythene films used to wrap them ('cling film') have led to its use at lower concentrations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Protec.

Diethyltoluamide *(BAN, rINN)*

DEET; *N,N*-Diethyl-3-methylbenzamide; Diethyltoluamide; Diethyltoluamidum; Dietiltoluamida; Диэтилтолуамид.
NN-Diethyl-*m*-toluamide.
$C_{12}H_{17}NO$=191.3
CAS — 134-62-3.
ATC — P03BX01.
ATC Vet — QP53GX01.
UNII — FB0C1XZV4Y.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Diethyltoluamide). A colourless liquid with a faint pleasant odour. Practically insoluble in water and in glycerol; miscible with alcohol, with carbon disulfide, with chloroform, with ether, and with isopropyl alcohol. Store in airtight containers.

Uses

Diethyltoluamide is an insect repellent that is effective against mosquitoes as well as blackflies, harvest-bugs or chiggers, midges, ticks, and fleas. It is considered to be of value for personal protection against malaria (p. 644.1). It has also been used as a repellent against leeches. It may be applied to skin and clothing. It is also used in veterinary practice as a fly repellent.

Adverse Effects and Precautions

Occasional hypersensitivity to diethyltoluamide has been reported. Diethyltoluamide should not be applied near the eyes, to mucous membranes, to broken skin, or to areas of skin flexion, as irritation or blistering may occur. Systemic toxicity has been reported after application of large topical doses, particularly in children.

Hypersensitivity and anaphylaxis has been described in a patient after exposure to diethyltoluamide.[1] Toxic encephalopathy has been noted in children given liberal applications of this compound;[2] seizures have also been reported,[3] and there have been cases of manic psychosis[4] and cardiovascular toxicity (sinus bradycardia and orthostatic hypotension)[5] associated with topical application. An assessment[6] of both published and unpublished data concluded that there had been remarkably few problems considering the widespread use of diethyltoluamide and that the encephalopathy in children had not been substantiated by detailed surveillance; however, another case analysis[7] did find an association with encephalopathy in children.

Toxic reactions, including death, have been reported after the ingestion of large amounts of diethyltoluamide-containing insect repellents.[8]

1. Miller JD. Anaphylaxis associated with insect repellent. *N Engl J Med* 1982; 307: 1341–2.
2. Roland HF, *et al.* Toxic encephalopathy in a child after brief exposure to insect repellents. *Can Med Assoc J* 1985; 132: 155–6.
3. Anonymous. Seizures temporally associated with use of DEET insect repellent—New York and Connecticut. *Arch Dermatol* 1989; 125: 1619–20.
4. Snyder JW, *et al.* Acute manic psychosis following the dermal application of N,N-diethyl-m-toluamide (DEET) in an adult. *J Toxicol Clin Toxicol* 1986; 24: 429–39.
5. Clem JR, *et al.* Insect repellent (N,N-diethyl-m-toluamide) cardiovascular toxicity in an adult. *Ann Pharmacother* 1993; 27: 289–93.
6. Goodyer L, Behrens RH. Short report: the safety and toxicity of insect repellents. *Am J Trop Med Hyg* 1998; 59: 323–4.
7. Briassoulis G, *et al.* Toxic encephalopathy associated with use of DEET insect repellents: a case analysis of its toxicity in children. *Hum Exp Toxicol* 2001; 20: 8–14.
8. Tenenbein M. Severe toxic reactions and death following the ingestion of diethyltoluamide-containing insect repellents. *JAMA* 1987; 258: 1509–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Kinderval RI; *Austral.*: Apex Repel; *Belg.*: Mouskito Tropical; *Canad.*: Muskol; Off Skintastic†; Off; Ungava; *Chile*: Repelex; *Fr.*: Biovectrol Tropique; Insect Ecran; *NZ*: Apex Repel Junior; Apex Repel Super with Sunscreen; Apex Repel Super; Repel Tropical Strength; *Swed.*: MyggA; *UK*: Bens; Jungle Formula Insect Repellent; Mijex; Mijex: Ultrathon.

Multi-ingredient Preparations. *Arg.*: Standard XXI; *Austral.*: Apex Repel Super†; Apex Repel Ultra; Apex Repel with Sunscreen; Apex Repel; *Belg.*: Mouskito Sun†; Mouskito Travel Milk†; Mouskito Travel Stick; *Ital.*: Sinezan; *Jpn*: Una Repellent†; *NZ*: Active Duty with Sunscreen; Active Duty; Apex Repel Super†; Apex Repel Ultra; *UK*: Autan.

Pharmacopoeial Preparations
USP 36: Diethyltoluamide Topical Solution.

Difenacoum

Difenacum; Дифенакум.
3-(3-Biphenyl-4-yl-1,2,3,4-tetrahydro-1-naphthyl)-4-hydroxycoumarin.
$C_{31}H_{24}O_3$=444.5
CAS — 56073-07-5.

NOTE. The name "superwarfarin" has been used to describe several anticoagulant rodenticides, including brodifacoum (p. 2149.2), bromadiolone (p. 2149.3), chlorophacinone (p. 2150.3), and difenacoum.

Profile

Difenacoum is an anticoagulant rodenticide.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 26/04/04)
2. WHO. Difenacoum health and safety guide. *IPCS Health and Safety Guide 95*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg095.htm (accessed 26/04/04)

Toxicity. Difenacoum, a second-generation anticoagulant rodenticide inhibits prothrombin synthesis to cause bleeding that may be occult.[1] It is absorbed from the gastrointestinal tract; dermal absorption is possible. Poisons containing 100 mg in each kg of bait are not hazardous to man; more concentrated forms are particularly hazardous and their availability should be restricted. Baits, which should be prepared only by trained personnel, should contain a suitable marker-dye.

There have been reports of poisoning with difenacoum.[2-4]

1. WHO. Safe use of pesticides: ninth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 720* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_720.pdf (accessed 21/07/08)
2. Barlow AM, *et al.* Difenacoum (Neosorexa) poisoning. *BMJ* 1982; 285: 541.
3. Butcher GP, *et al.* Difenacoum poisoning as a cause of haematuria. *Hum Exp Toxicol* 1992; 11: 553–4.
4. McCarthy PT, *et al.* Covert poisoning with difenacoum: clinical and toxicological observations. *Hum Exp Toxicol* 1997; 16: 166–70.

Diflubenzuron

Дифлубензурон.
1-(4-Chlorophenyl)-3-(2,6-difluorobenzoyl)urea.
$C_{14}H_9ClF_2N_2O_2$=310.7
CAS — 35367-38-5.
ATC Vet — QP53BC02.
UNII — J76U6ZSI8D.

Profile

Diflubenzuron is an insecticide and larvicide that acts as a growth regulator by interfering with the formation of cuticle. It is used in agriculture and for the control of disease vectors. It is also used in veterinary practice for its activity against flies and lice.

Diflubenzuron possesses residual activity against mosquito larvae.

1. WHO. Diflubenzuron. health and safety guide. *IPCS Health and Safety Guide 99*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg099.htm (accessed 26/04/04)
2. WHO. Diflubenzuron. *Environmental Health Criteria 184*. Geneva: WHO, 1996. Available at: http://www.inchem.org/documents/ehc/ehc/ehc184.htm (accessed 26/04/04)

Dimethoate

Dimetoato; Fosfamid; Диметоат; Фосфамид.
O,O-Dimethyl *S*-methylcarbamoylmethyl phosphorodithioate.
$C_5H_{12}NO_3PS_2$=229.2
CAS — 60-51-5.
UNII — W6U08B045O.

Profile

Dimethoate is an organophosphorus insecticide (p. 2158.3) used in agriculture.

1. WHO. Dimethoate health and safety guide. *IPCS Health and Safety Guide 20*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg020.htm (accessed 28/05/04)
2. WHO. Dimethoate. *Environmental Health Criteria 90*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc90.htm (accessed 28/05/04)
3. Jovanović D, *et al.* A case of unusual suicidal poisoning by the organophosphorus insecticide dimethoate. *Hum Exp Toxicol* 1990; 9: 49–51.
4. Hoffmann U, Papendorf T. Organophosphate poisonings with parathion and dimethoate. *Intensive Care Med* 2006; 32: 464–8.
5. Eddleston M, *et al.* Relationship between blood alcohol concentration on admission and outcome in dimethoate organophosphorus self-poisoning. *Br J Clin Pharmacol* 2009; 68: 916–19.

Dimethyl Phthalate

Dimetilo, ftalato de; DMP; Methyl Phthalate; Диметилфталат.
Dimethyl benzene-1,2-dicarboxylate.
$C_{10}H_{10}O_4$=194.2
CAS — 131-11-3.
ATC — P03BX02.
ATC Vet — QP53GX02.
UNII — 08X7F5UDJM.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Dimethyl Phthalate). A colourless or faintly coloured liquid, odourless or almost odourless. Slightly soluble in water; miscible with alcohol, with ether, and with most organic solvents.

Uses

Dimethyl phthalate is an insect repellent.

1. Kamrin MA. Phthalate risks, phthalate regulation, and public health: a review. *J Toxicol Environ Health B* 2009; 12: 157–74.

Adverse Effects and Precautions

Dimethyl phthalate may cause temporary smarting and should not be applied near the eyes or to mucous membranes. As with other phthalates contact with plastics should be avoided.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Novascabin.

Dimpylate *(BAN, rINN)*

Diazinon; Diazynon; Dimpilato; Dimpylaatti; Dimpylat; Dimpylatum; Димпилат.
O,O-Diethyl *O*-(2-isopropyl-6-methylpyrimidin-4-yl) phosphorothioate.
$C_{12}H_{21}N_2O_3PS$=304.3
CAS — 333-41-5.
ATC Vet — QP53AF03.
UNII — YUS1M1Q929.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Dimpylate). A clear, yellowish-brown, slightly viscous liquid. Practically insoluble in water; miscible with alcohol, with ether, and with most organic solvents.

Profile

Dimpylate is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal. It is also used as an insecticide in agriculture and horticulture.

1. Wagner SL, Orwick DL. Chronic organophosphate exposure associated with transient hypertonia in an infant. *Pediatrics* 1994; 94: 94–7.

Dinitro-o-cresol

DNOC; Динитро-о-крезол.
4,6-Dinitro-o-cresol.
$C_7H_6N_2O_5$=198.1
CAS — 534-52-1.
UNII — 1604ZJR09T.

Profile

Dinitro-*o*-cresol is a dinitrophenol formerly used as an insecticide and herbicide. It increases metabolism by uncoupling oxidative phosphorylation and was also formerly used in obesity. Fatal poisoning has occurred.

References.

1. WHO. Dinitro-ortho-cresol. *Environmental Health Criteria 220.* Geneva: WHO, 2000. Available at: http://www.inchem.org/documents/ehc/ehc/ehc220.htm (accessed 26/04/04)

Dinitrophenol

Dinitrofenol; DNP; Динитрофенол.
2,4-Dinitrophenol.
$C_6H_4N_2O_5$=184.1
CAS — 51-28-5.
UNII — Q13SKS21MN.

Profile

Dinitrophenol has been used as a herbicide. Since dinitrophenol increases metabolism by uncoupling oxidative phosphorylation it was formerly used in the treatment of obesity. Fatal poisoning has occurred.

Dioxation *(BAN, rINN)*

Dioxathion; Dioxatión; Dioxationum; Диоксатион.
It consists mainly of *cis* and *trans* isomers of *S,S'*-1,4-dioxan-2,3-diyl bis(*O,O*-diethyl phosphorodithioate).
$C_{12}H_{26}O_6P_2S_4$=456.5
CAS — 78-34-2.
UNII — J2DF82JA7N.

Profile

Dioxation is an organophosphorus insecticide (p. 2158.3) that has been used in agriculture and as a topical ectoparasiticide in veterinary practice.

Diphenadione *(BAN, pINN)*

Difenadiona; Diphacinone; Diphénadione; Diphenadionum; Дифенадион.
2-(Diphenylacetyl)indan-1,3-dione.
$C_{23}H_{16}O_3$=340.4
CAS — 82-66-6.
ATC — B01AA10.
ATC Vet — QB01AA10.
UNII — 54CA01C6JX.

Profile

Diphenadione is used as an anticoagulant rodenticide.

Diquat Dibromide

Diquat, dibromuro de; Дикват Дибромид.
9,10-Dihydro-8a,10a-diazoniaphenanthrene dibromide; 1,1'-Ethylene-2,2'-bipyridyldiylium dibromide.
$C_{12}H_{12}Br_2N_2$=344.0
CAS — 2764-72-9 (diquat); 85-00-7 (diquat dibromide).
UNII — 68DV3T272W.

Profile

Diquat dibromide is a contact herbicide used in agriculture and horticulture. It has similar adverse effects to those of paraquat (p. 2159.1).

References.

1. WHO. Paraquat and diquat. *Environmental Health Criteria 39.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc39.htm (accessed 26/04/04)
2. WHO. Diquat health and safety guide. *IPCS Health and Safety Guide 52.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg052.htm (accessed 26/04/04)
3. Proudfoot A, ed. Pesticide poisoning: notes for the guidance of medical practitioners. 2nd ed. London: DoH, The Stationery Office, 1996.
4. Jones GM, Vale JA. Mechanisms of toxicity, clinical features, and management of diquat poisoning: a review. *J Toxicol Clin Toxicol* 2000; 38: 123–8.

Emamectin

Emamectina; Эмамектин.
A mixture of (4″*R*)-5-*O*-Demethyl-4″-deoxy-4″-(methylamino)avermectin A_{1a} and (4″*R*)-5-*O*-Demethyl-25-de(1-methylpropyl)-4″-deoxy-4″-(methylamino)-25-(1-methylethyl)avermectin A_{1a} in the ratio of 9:1.
CAS — 121124-29-6 (major component); 121424-52-0 (minor component); 137335-79-6.
ATC Vet — QP54AA06.
UNII — 8C43881H4W.

Profile

Emamectin is an avermectin insecticide used for the control of sea-lice infestation in salmon.

Endod

CAS — 39278-85-8.

Profile

Endod is obtained from the dried fruits of *Phytolacca dodecandra* (Phytolaccaceae) and has molluscicidal properties. It has been investigated for the control of the snail vector of schistosomiasis.

Endosulfan

Endosulfán; Эндосульфан.
1,4,5,6,7,7-Hexachloro-8,9,10-trinorborn-5-en-2,3-ylenebismethylene sulphite.
$C_9H_6Cl_6O_3S$=406.9
CAS — 115-29-7.
UNII — QY5Y9R7G0E.

Profile

Endosulfan is a chlorinated insecticide (p. 2150.2) used in agriculture.

References.

1. WHO. Endosulfan. *Environmental Health Criteria 40.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc40.htm (accessed 26/04/04)
2. WHO. Endosulfan health and safety guide. *IPCS Health and Safety Guide 17.* Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg017.htm (accessed 26/04/04)
3. Blanco-Coronado JL, *et al.* Acute intoxication by endosulfan. *J Toxicol Clin Toxicol* 1992; 30: 575–83.
4. Boerboom FT, *et al.* Nonaccidental endosulfan intoxication: a case report with toxicokinetic calculations and tissue concentrations. *J Toxicol Clin Toxicol* 1998; 36: 345–52.
5. Chugh SN, *et al.* Endosulfan poisoning in Northern India: a report of 18 cases. *Int J Clin Pharmacol Ther* 1998; 36: 474–7.
6. Venkateswarlu K, *et al.* Endosulfan poisoning—a clinical profile. *J Assoc Physicians India* 2000; 48: 323–5.
7. Karatas AD, *et al.* Characteristics of endosulfan poisoning: a study of 23 cases. *Singapore Med J* 2006; 47: 1030–2.
8. Bektas M, *et al.* Management of acute endosulfan poisoning in an organophosphate poisoning clinic. *Clin Toxicol* 2007; 45: 563–4.
9. Durukan P, *et al.* Experiences with endosulfan mass poisoning in rural areas. *Eur J Emerg Med* 2009; 16: 53–6.
10. Moon JM, Chun BJ. Acute endosulfan poisoning: a retrospective study. *Hum Exp Toxicol* 2009; 28: 309–16.

Endrin

Endrin; Endryna; Эндрин.
(1*R*,4*S*,4a*S*,5*S*,6*S*,7*R*,8*R*,8a*R*)-1,2,3,4,10,10-Hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene.
$C_{12}H_8Cl_6O$=380.9
CAS — 72-20-8.
UNII — 0B9NVE7YCL.

Profile

Endrin is a chlorinated insecticide (p. 2150.2), but its use was prohibited, at least in some countries, because of toxicity and persistence in the environment.

General references to endrin,[1-4] including reports of poisoning.[2,3]

1. Anonymous. Acute convulsions associated with endrin poisoning—Pakistan. *JAMA* 1985; 253: 334–5.
2. Runhaar EA, *et al.* A case of fatal endrin poisoning. *Hum Toxicol* 1985; 4: 241–7.
3. WHO. Endrin health and safety guide. *IPCS Health and Safety Guide 60.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg060.htm (accessed 26/04/04)
4. WHO. Endrin. *Environmental Health Criteria 130.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc130.htm (accessed 26/04/04)

Esdepallethrine

Esdepaletrina; Эсдепалетрин.
(*S*)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)-cyclopropanecarboxylate
$C_{19}H_{26}O_3$=302.4
CAS — 28434-00-6.

Profile

Esdepallethrine is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1). It is used as an acaricide with piperonyl butoxide (p. 2160.2) in the topical treatment of scabies (p. 2148.1).

Esdepallethrine is also used in devices and sprays to control insects, including mosquitoes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Spregal; *Gr.*: Spregal; *Israel*: Acardust; *Neth.*: Spregal; *Rus.*: Spregal (Спрегаль); *S.Afr.*: Spregal; *Ukr.*: Spregal (Спрегаль).

Ethion

Diethion; Etión; Ethion; Этион.
O,O,O',O'-Tetraethyl *S,S'*-methylenediphosphorodithioate.
$C_9H_{22}O_4P_2S_4$=384.5
CAS — 563-12-2.
UNII — 2TI07NO12Y.

Profile

Ethion is an organophosphorus insecticide used as a topical ectoparasiticide in veterinary practice.

Ethohexadiol

Ethylhexanediol; Etohexadiol; Rutgers-612; Этогексадиол.
2-Ethylhexane-1,3-diol.
$C_8H_{18}O_2$=146.2
CAS — 94-96-2.
ATC — P03BX06.
ATC Vet — QP53GX04.
UNII — M9JGK7U88V.

Profile

Ethohexadiol is an insect repellent. It may be applied topically to the skin and to clothing. It has been used with dimethyl phthalate.

Ethyl Butylacetylaminopropionate

EBAAP; IR-3535; Merck-3535; Repellent 3535.
(*N*-Butyl-*N*-acetyl)-3-ethylaminopropionate; *N*-Acetyl-*N*-butyl-beta-alanine ethyl ester.
$C_{11}H_{21}NO_3$=215.3
CAS — 52304-36-6.
UNII — 65GQA237EH.

Profile

Ethyl butylacetylaminopropionate is used as an insect repellent; it may be applied to the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hyalpur Moustique; *Bel.*: Mouskito; Shampoux Repel; *Braz.*: Johnson's Baby Loção Anti-Mosquito; *Fr.*: Biovectrol Famille; Cinq sur Cinq; Pa à Repulsif†; Prebutix; *Thai.*: Johnson's Baby Clear; *UK*: Mijex Extra.

Multi-ingredient Preparations. *Arg.*: Standard XXI; *Austria*: Apex Repel Ultra; Apex Repel with Sunscreen; Apex Repel; *Belg.*: Mouskito Sun†; *Fr.*: Mousticologne†; *Mon.*: Akipic; *NZ*: Active Duty with Sunscreen; Apex Repel Super†; Apex Repel Ultra.

Ethylene Dibromide

Dibromoetano; EDB; Etileno, dibromuro de; Этилена Дибромид.
1,2-Dibromoethane.
$C_2H_4Br_2$=187.9
CAS — 106-93-4.
UNII — 1N41638RNO.

Profile

Ethylene dibromide is an insecticidal fumigant and a lead scavenger used in the petroleum industry. Its use has been restricted in certain areas because of carcinogenicity in *animals* and because of evidence of persistence in fruit and cereals that have undergone fumigation.

Ethylene dibromide is more toxic than carbon tetrachloride or ethylene dichloride. It is irritant to the eyes, skin, and mucous membranes. Inhalation leads to drowsiness, CNS depression, and possibly pulmonary oedema. Contact with the skin causes blistering and it is readily absorbed. Kidney and liver damage may occur.

Reports[1-4] of poisoning due to ethylene dibromide.

1. Letz GA, *et al.* Two fatalities after acute occupational exposure to ethylene dibromide. *JAMA* 1984; 252: 2428–31.
2. Singh S, *et al.* Non-fatal ethylene dibromide ingestion. *Hum Exp Toxicol* 2000; 19: 152–3.
3. Mehrotra P, *et al.* Two cases of ethylene dibromide poisoning. *Vet Hum Toxicol* 2001; 43: 91–2.
4. Singh N, *et al.* Outcome of sixty four cases of ethylene dibromide ingestion treated in tertiary care hospital. *J Assoc Physicians India* 2007; 55: 842–5.

Ethylene Dichloride

Brocide; Dicloroetano; Dutch Liquid; Etileno, dicloruro de; Этилен Дихлорид.

1,2-Dichloroethane.

$C_2H_4Cl_2$=98.95

CAS — 107-06-2.

UNII — 55163UI47.

Profile

Ethylene dichloride is an insecticidal fumigant. It is also used in the petroleum industry and as an industrial solvent. Exposure to the vapour may cause lachrymation and corneal clouding, nasal irritation, and vertigo due to the depressant effect on the CNS. Contact with the skin may cause dermatitis. Kidney and liver damage, hypotension and cardiac impairment, gastrointestinal disturbances, haemorrhage, coma, and pulmonary oedema may follow absorption after inhalation, topical application, or ingestion.

Ethylene dichloride has been reported to be carcinogenic in *animals*.

References.

1. WHO. 1,2-Dichloroethane health and safety guide. *IPCS Health and Safety Guide 55.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg055.htm (accessed 26/04/04)
2. WHO. 1,2 Dichloroethane. *Environmental Health Criteria 176.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc176.htm (accessed 06/06/06)
3. Proudfoot A, ed. Pesticide poisoning: notes for the guidance of medical practitioners. 2nd ed. London: DoH, The Stationery Office, 1996.

Etofenprox *(rINN)*

Ethofenprox; Étofenprox; Etofenproxum; Этофенпрокс.

α-[(*p*-Ethoxy-β,β-dimethylphenethyl)oxy]-*m*-phenoxytoluene.

$C_{25}H_{28}O_3$=376.5

CAS — 80844-07-1.

UNII — 0LD7P9153C.

Profile

Etofenprox is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in the vector control of malaria (p. 644.1).

Famphur

Famfur; Famophos; Фамфур.

$C_{10}H_{16}NO_5PS_2$=325.3

CAS — 52-85-7.

UNII — 02UOP4Z000.

Profile

Famphur is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal.

Fenitrothion *(BAN)*

Fenitrotión; Фенитротион.

O,O-Dimethyl *O*-4-nitro-*m*-tolyl phosphorothioate.

$C_9H_{12}NO_5PS$=277.2

CAS — 122-14-5.

UNII — W8M4X3Y7ZY.

Profile

Fenitrothion is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice. It is also used as an agricultural insecticide.

References.

1. WHO. Fenitrothion health and safety guide. *IPCS Health and Safety Guide 63.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg065.htm (accessed 26/04/04)
2. WHO. Fenitrothion. *Environmental Health Criteria 133.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc133.htm (accessed 26/04/04)
3. Bouma MJ, Nesbit R. Fenitrothion intoxication during spraying operations in the malaria programme for Afghan refugees in North West Frontier Province of Pakistan. *Trop Geogr Med* 1995; 47: 12–14.
4. Inoue S, *et al.* Prognostic factors and toxicokinetics in acute fenitrothion self-poisoning requiring intensive care. *Clin Toxicol* 2008; 46: 528–33.

Fenthion *(BAN)*

Bayer 29493; Fention; S-752; Фентион.

O,O-Dimethyl *O*-4-methylthio-*m*-tolyl phosphorothioate.

$C_{10}H_{15}O_3PS_2$=278.3

CAS — 55-38-9.

ATC Vet — QP53BB02.

UNII — BL0L45OVKT.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Fenthion). A yellowish-brown oily substance. Immiscible with water; miscible with alcohol and with chloroform.

Profile

Fenthion is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal. Fenthion has also been used in agriculture.

Toxicity. Macular changes have been detected in the eyes of workers regularly exposed to fenthion.[1] It was considered that there was a need for long-term studies on subjects exposed to different organophosphorus compounds to assess their role in producing macular changes.

1. Misra UK, *et al.* Some observations on the macula of pesticide workers. *Hum Toxicol* 1985; 4: 135–45.

Fenvalerate *(BAN)*

Fenvalerato; Fenwalerianian; OMS-2000; Pydrin; S-5602; SD-43775; WL-43775; Фенвалерат.

(*RS*)-α-Cyano-3-phenoxybenzyl (*RS*)-2-(4-chlorophenyl)-3-methylbutyrate.

$C_{25}H_{22}ClNO_3$=419.9

CAS — 51630-58-1.

ATC Vet — QP53AC14; QP53AX02.

UNII — Z6MXZ39302.

Profile

Fenvalerate is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used as a topical ectoparasiticide in veterinary practice. It has also been used as an insecticide in agriculture and horticulture.

Esfenvalerate, one of the stereoisomers of fenvalerate, is also used as an agricultural insecticide.

References.

1. WHO. Fenvalerate health and safety guide. *IPCS Health and Safety Guide 34.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg034.htm (accessed 26/04/04)
2. WHO. Fenvalerate. *Environmental Health Criteria 95.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc95.htm (accessed 26/04/04)

Fipronil *(BAN)*

Fipronilil; Fipronilo; MB-46030; RM-1601; Фипронил.

(*RS*)-5-Amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-(trifluoromethylsulfinyl)pyrazole-3-carbonitrile.

$C_{12}H_4Cl_2F_6N_4OS$=437.1

CAS — 120068-37-3.

ATC Vet — QP53AX15.

UNII — QGH063955F.

Profile

Fipronil is used as a topical ectoparasiticide in veterinary practice. It has also been investigated for the treatment of head lice.

Flocoumafen

Flocoumafene; Flocumafeno; OMS-3047; Флокумафен.

4-Hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl]coumarin.

$C_{33}H_{25}F_3O_4$=542.6

CAS — 90035-08-8.

Profile

Flocoumafen is a coumarin derivative used as an anticoagulant rodenticide. It is said to be effective in rodents resistant to other anticoagulant rodenticides.

References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 26/04/04)

Fluazuron *(rINN)*

CGA-157419; Fluazurón; Fluazuronum; Флуазурон.

1-(4-Chloro-3-[[3-chloro-5-(trifluoromethyl)-2-pyridyl]oxy]phenyl)-3-(2,6-difluorobenzoyl)urea.

$C_{20}H_{10}Cl_2F_5N_3O_3$=506.2

CAS — 86811-58-7.

UNII — VB0PV6I7L6.

Profile

Fluazuron is used as a topical ectoparasiticide in veterinary practice.

Flumethrin *(BAN)*

Flumethrinum; Flumetriini; Flumetrin; Flumetrina; Флуметрин.

α-Cyano-4-fluoro-3-phenoxybenzyl 3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate.

$C_{28}H_{22}Cl_2FNO_3$=510.4

CAS — 69770-45-2.

ATC Vet — QP53AC05.

Profile

Flumethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used as a topical ectoparasiticide in veterinary practice.

A report[1] of poisoning with flumethrin.

1. Box SA, Lee MR. A systemic reaction following exposure to a pyrethroid insecticide. *Hum Exp Toxicol* 1996; 15: 389–90.

Fluoroacetamide

Compound 1081; Fluoroacetamida; Фторацетамид.

FCH_2CONH_2=77.06

CAS — 640-19-7.

UNII — B18R611M38.

Profile

Fluoroacetamide is a rodenticide and produces adverse effects similar to those of sodium fluoroacetate (p. 2161.3).

Fluvalinate

Fluvalinato; ZR-3210; Флювалинат.

Cyano(3-phenoxyphenyl)methyl ester of *N*-[2-chloro-4-(trifluoromethyl)phenyl]-DL-valine.

$C_{26}H_{22}ClF_3N_2O_3$=502.9

CAS — 69409-94-5.

ATC Vet — QP53AC10.

UNII — 364G5G03VC.

Profile

Fluvalinate is a pesticide used in beekeeping.

Glyphosate

Glifosato; Glyfosato; Глифосат.

N-(Phosphonomethyl)glycine.

$C_3H_8NO_5P$=169.1

CAS — 1071-83-6.

UNII — 4632WW1X5A.

Profile

Glyphosate is used as a herbicide.

References.

1. WHO. Glyphosate. *Environmental Health Criteria 159.* Geneva: WHO, 1994. Available at: http://www.inchem.org/documents/ehc/ehc/ehc159.htm (accessed 26/04/04)

Toxicity. Reports[1-5] and reviews[6] of poisoning with glyphosate products, prognostic factors,[7] guidelines for treatment[8] have been published. The toxicity has been believed to be largely due to the inclusion of surfactants, particularly polyoxyethyleneamine, in the herbicide (Roundup) formulation but products vary considerably as to the surfactant contained and the concentration and salt of glypho-

sate used, and the evidence that surfactants potentiate glyphosate toxicity is unclear.[8]

1. Sawada Y, *et al.* Probable toxicity of surface-active agent in commercial herbicide containing glyphosate. *Lancet* 1988; i: 299.
2. Talbot AR, *et al.* Acute poisoning with a glyphosate-surfactant herbicide ('Roundup'): a review of 93 cases. *Hum Exp Toxicol* 1991; 10: 1–8.
3. Menkes DB, *et al.* Intentional self-poisoning with glyphosate-containing herbicides. *Hum Exp Toxicol* 1991; 10: 103–7.
4. Chen YJ, *et al.* The epidemiology of glyphosate-surfactant herbicide poisoning in Taiwan, 1986-2007: a poison center study. *Clin Toxicol* 2009; 47: 670–7.
5. Roberts DM, *et al.* A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning. *Clin Toxicol* 2010; 48: 129–36.
6. Bradberry SM, *et al.* Glyphosate poisoning. *Toxicol Rev* 2004; 23: 159–67.
7. Lee CH, *et al.* The early prognostic factors of glyphosate-surfactant intoxication. *Am J Emerg Med* 2008; 26: 275–81.
8. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners.* 2nd ed. London: DoH, The Stationery Office, 1996.

Heptachlor

Heptacloro; Гептахлор.

1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene.

$C_{10}H_5Cl_7$=373.3

CAS — 76-44-8.

UNII — 7GLS9ACN3L.

Profile

Heptachlor is a chlorinated insecticide (p. 2150.2), but its use was prohibited, at least in some countries, because of its persistent nature.

References.

1. WHO. Heptachlor. *Environmental Health Criteria 38.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc38.htm (accessed 26/04/04)
2. WHO. Heptachlor health and safety guide. *IPCS Health and Safety Guide 14.* Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg014.htm (accessed 26/04/04)

Heptenophos

Heptenofós; Hoe-02982; Хептенофос.

7-Chlorobicyclo[3.2.0]hepta-2,6-dien-6-yl dimethyl phosphate.

$C_9H_{12}ClO_4P$=250.6

CAS — 23560-59-0.

Profile

Heptenophos is an organophosphorus insecticide (p. 2158.3) that has been used in veterinary practice for the control of ectoparasites. It is also used in agriculture.

Hexachlorobenzene

HCB; Heksachlorobenzen; Hexaclorobenceno; Гексахлорбензол.

C_6Cl_6=284.8

CAS — 118-74-1.

UNII — 4Z87H0LKUY.

NOTE. Hexachlorobenzene should not be confused with gamma benzene hexachloride (lindane).

Profile

Hexachlorobenzene has been used as an agricultural fungicide. It is not biodegradable to any significant extent and hexachlorobenzene residues in food have arisen as a result of its occurrence in industrial wastes as well as its use as a fungicide; its use is banned in some countries.

Hexachlorobenzene is reported to be distributed into breast milk.

References.

1. WHO. Hexachlorobenzene. *Environmental Health Criteria 195.* Geneva: WHO, 1997. Available at: http://www.inchem.org/documents/ehc/ehc/ehc195.htm (accessed 26/04/04)
2. WHO. Hexachlorobenzene health and safety guide. *IPCS Health and Safety Guide 107.* Geneva: WHO, 1998. Available at: http://www.inchem.org/documents/hsg/hsg/hsg107.htm (accessed 26/04/04)
3. Reed L, *et al.* Environmental toxicology and health effects associated with hexachlorobenzene exposure. *Rev Environ Health* 2007; 22: 213–43.

Toxicity. Porphyria cutanea tarda[1] and parkinsonism[2] have both been reported in subjects who had ingested seed crops treated with hexachlorobenzene. In a further report the symptoms of porphyria in some patients have been said to persist for many years.[3]

1. Cam C, Nigogosyan G. Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. *JAMA* 1963; 183: 88–91.
2. Chapman LJ, *et al.* Parkinsonism and industrial chemicals. *Lancet* 1987; i: 332–3.
3. Cripps DJ, *et al.* Porphyria turcica due to hexachlorobenzene: a 20 to 30 year follow-up study on 204 patients. *Br J Dermatol* 1984; 111: 413–22.

Hydrocyanic Acid

Ácido hidrociánico; Ácido prúsico; Cianhídrico, ácido; Prussic Acid; Синильная Кислота; Цианисто-водородная Кислота.

CAS — 74-90-8.

Description. Hydrocyanic acid is an aqueous solution containing hydrogen cyanide, HCN = 27.03. A colourless liquid with a characteristic almond odour.

Uses

Cyanides have various industrial applications. Hydrocyanic acid and cyanide salts produce hydrogen cyanide, which has been used as a gas for the eradication of rabbits, rodents, and some other pests. Cyanide salts that might be encountered include calcium cyanide, mercuric cyanide, potassium cyanide, potassium ferricyanide, potassium sodium cyanide, and sodium cyanide.

Adverse Effects and Precautions

Hydrocyanic acid and its vapour are intensely poisonous. Cyanides interfere with the oxygen uptake of cells by inhibition of cytochrome oxidase, an enzyme necessary for cellular oxygen transport.

Poisoning by cyanides may occur from inhalation of the vapour, ingestion, or absorption through the skin. Poisoning may arise from cyanide pesticides, industrial accidental exposure, or the inhalation of fumes from some burning plastics. Poisoning may also occur from cyanide-containing plants or fruits.

When large doses of hydrocyanic acid are taken, unconsciousness occurs within a few seconds and death within a few minutes. With smaller toxic doses the symptoms, which occur within a few minutes, may include constriction of the throat, nausea, vomiting, giddiness, headache, palpitation, hyperpnoea then dyspnoea, bradycardia (although initially there may be tachycardia), unconsciousness, and violent convulsions, followed by death. The characteristic smell of bitter almonds may not be obvious and not all individuals can detect it. Cyanosis is not prominent. Similar but usually slower effects occur with cyanide salts.

The fatal dose of hydrocyanic acid for man is considered to be about 50 mg and of the cyanides about 250 mg.

Treatment of Adverse Effects

Cyanide is highly toxic. It is absorbed very rapidly on inhalation and the poisoned patient should be removed from the area and given oxygen. Steps should be taken to ensure that the airway is adequate. In cases of dermal exposure, contaminated clothing should be removed and the skin washed thoroughly with soap and water. When cyanide has been ingested, gastric lavage or activated charcoal may be considered if the patient presents within 1 hour. Appropriate measures should be instituted to correct hypotension and acidosis. The choice of an antidote depends on the severity of the poisoning, certainty of diagnosis, and the cause.

In some countries cyanide antidote kits containing amyl nitrite, sodium nitrite, and sodium thiosulfate are available. In conscious patients, amyl nitrite (p. 1540.2) may be inhaled until intravenous access is established. Intravenous injection of sodium nitrite (p. 1574.3) is then followed immediately by intravenous sodium thiosulfate (p. 1576.2). The nitrite components from amyl nitrite and sodium nitrite convert haemoglobin to methaemoglobin which competes with cytochrome oxidase for cyanide, with the formation of cyanmethaemoglobin; sodium thiosulfate acts as a sulfur donor and aids the conversion or inactivation of cyanide from cyanmethaemoglobin to thiocyanate. The methaemoglobinaemia induced by the nitrites in the antidote kits can be dangerous and fatalities have been reported.

The UK *National Poisons Information Service* recommends that intravenous sodium thiosulfate be used alone in mild poisoning. The preferred treatment for those with moderate to severe poisoning is intravenous dicobalt edetate (p. 1548.3) since it forms a stable complex with the cyanide ion. However, cyanide poisoning should be confirmed, as absence of cyanide puts the patient at risk from the adverse effects of dicobalt edetate. Each dose of dicobalt edetate may be followed immediately by intravenous injection of glucose 50% to reduce cobalt toxicity; in cases of proven cyanide toxicity glucose is unnecessary but is generally given as a precaution. Sodium thiosulfate alone (in cases of moderate poisoning) or sodium nitrite followed by sodium thiosulfate (in cases of severe poisoning) are alternative treatment options if dicobalt edetate is not available.

Hydroxocobalamin (p. 2108.1) may be used intravenously for the management of cyanide toxicity, particularly for victims of smoke inhalation, and an antidote kit is available in some countries for this purpose.

Some references concerning the management of cyanide poisoning.[1-7] The use of solutions A and B (15.8% ferrous sulfate in 0.3% citric acid, and 6% sodium carbonate respectively) as so called oral antidotes in persons exposed to cyanide has been condemned as ineffective and lacking scientific evidence.[2]

1. Langford RM, Armstrong RF. Algorithm for managing injury from smoke inhalation. *BMJ* 1989; 299: 902–5.
2. Koizumi A. Fighting myths. *Lancet* 1994; 344: 559–60.
3. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners.* 2nd ed. London: DoH, The Stationery Office, 1996.
4. Geller RJ, *et al.* Pediatric cyanide poisoning: causes, manifestation, management, and unmet needs. *Pediatrics* 2006; 118: 2146–58.
5. Baud FJ. Cyanide: critical issues in diagnosis and treatment. *Hum Exp Toxicol* 2007; 26: 191–201.
6. Shepherd G, Velez LI. Role of hydroxocobalamin in acute cyanide poisoning. *Ann Pharmacother* 2008; 42: 661–9.
7. Hall AH, *et al.* Which cyanide antidote? *Crit Rev Toxicol* 2009; 39: 541–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Rus.*: Tonginal (Тонгинал); *Ukr.*: Tonginal (Тонгинал).

Icaridin *(rINN)*

Hepidanin; Icaridina; Icaridine; Icaridinum; KBR-3023 Picaridan; Picaridin; Икаридин.

1-Methylpropyl 2-(2-hydroxyethyl)piperidine-1-carboxylate.

$C_{12}H_{23}NO_3$=229.3

CAS — 119515-38-7.

UNII — N51GQX0837.

NOTE. Bayrepel and Saltidin are trade names that have been used for icaridin.

Profile

Icaridin is an insect repellent that is reported to be effective against mosquitoes, flies, and ticks.

References.

1. Scheinfeld N. Picaridin: a new insect repellent. *J Drugs Dermatol* 2004; 3: 59–60.
2. Anonymous. Picardin—a new insect repellent. *Med Lett Drugs Ther* 2004; 47: 46–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Apex Repel New Era; *Fr.*: Insect Ecran; *Malaysia*: Moz Away Junior; Moz Away Long Hour Protection; *NZ*: Apex Repel New Era; *Singapore*: Moz Away; *USA*: Cutter Advanced.

Multi-ingredient Preparations. *Fr.*: Mousticologne†; *UK*: Autan.

Imidacloprid

Bay-NTN-33893; Имидаклоприд.

1-[(6-Chloro-3-pyridinyl)methyl]-4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine.

$C_9H_{10}ClN_5O_2$=255.7

CAS — 105827-78-9; 138261-41-3.

ATC Vet — QP53AX17.

UNII — 3BN7M937V8.

Profile

Imidacloprid is used as a topical ectoparasiticide in veterinary practice, and as an insecticide in agriculture. It has also been investigated for use in the treatment of headlice.

Iodofenphos *(BAN)*

Iodofenfós; Jodfenphos; Иодофенфос.

O-2,5-Dichloro-4-iodophenyl *O,O*-dimethyl phosphorothioate.

$C_8H_8Cl_2IO_3PS$=413.0

CAS — 18181-70-9.

UNII — SME6G1846X.

Profile

Iodofenphos is an organophosphorus insecticide (p. 2158.3) used in veterinary practice for the control of ectoparasites in the environment. It has also been used as an agricultural insecticide. It is an effective mosquito larvicide.

Iodopropynyl Butyl Carbamate

Iodocarb; IPBC; Йодопропинил Бутилкарбамат.

3-Iodo-2-propynyl-*N*-butyl carbamate.

$C_8H_{12}INO_2$=281.1

CAS — 55406-53-6.

UNII — 603P14DHEB.

Profile

Iodopropynyl butyl carbamate is a carbamate pesticide (p. 2149.3). It is used as a preservative in cosmetic preparations; contact sensitisation has been reported. It is also used as a wood preservative.

References.
1. Bryld LE, *et al.* Iodopropynyl butylcarbamate: a new contact allergen. *Contact Dermatitis* 1997; 36: 156–8.
2. Badreshia S, Marks JG. Iodopropynyl butylcarbamate. *Am J Contact Dermat* 2002; 13: 77–9.
3. Davis RF, Johnston GA. Iodopropynyl butylcarbamate contact allergy from wood preservative. *Contact Dermatitis* 2007; 56: 112.
4. Natkunarajah J, *et al.* Allergic contact dermatitis to iodopropynyl butylcarbamate found in a cosmetic cleansing wipe. *Contact Dermatitis* 2008; 58: 316–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Effaclar Gel Moussant Purifiant.

Multi-ingredient Preparations. *Braz.*: Effaclar; Pityval; Saliker; *Chile*: Effaclar Agua Desmaquillante Purificante; Effaclar AI; Effaclar K; Normaderm Exfoliante; Normaderm Gel de Limpieza; Normaderm Tonico Astringente; Podexine Anti-Transpirante; *Fr.*: Effaclar K; Pityval†; *Irl.*: Effaclar AI; Effaclar K; Effaclar.

Lindane *(BAN, USAN, rINN)*

666; Benhexachlor; Gamma Benzene Hexachloride; Gamma-BHC; Gamma-HCH; HCH; Hexicide; Lindaani; Lindan; Lindán; Lindanas; Lindano; Lindanum; Линдан.

1α,2α,3β,4α,5α,6β-Hexachlorocyclohexane.

$C_6H_6Cl_6$=290.8

CAS — 58-89-9.

ATC — P03AB02.

ATC Vet — QP53AB02; QS02QA01.

UNII — 59NEE7PCAB.

Pharmacopoeias. In *Chin.*, *Int.*, and *US.*

USP 36: (Lindane). A white, crystalline powder with a slight musty odour. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in chloroform; sparingly soluble in ether; slightly soluble in ethylene glycol.

Uses and Administration

Lindane is a chlorinated insecticide (p. 2150.2). It has been used topically in a concentration of 1% for scabies (p. 2148.1) in selected patients and has also been used in pediculosis (p. 2147.3), but use for head lice is restricted by resistance.

Lindane has been used for the control of disease vectors including mosquitoes, lice, and fleas, but resistance has developed. It has also been used as an agricultural and a horticultural insecticide, but its use is prohibited or restricted in many countries.

References.
1. WHO. Lindane. *Environmental Health Criteria 124*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc124.htm (accessed 26/04/04)
2. WHO. Lindane health and safety guide. *IPCS Health and Safety Guide 54*. Geneva: WHO. 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg054.htm (accessed 26/04/04)

Adverse Effects, Treatment, and Precautions

As for Chlorinated Insecticides, p. 2150.2.

Serious adverse effects, including seizures and deaths, have been reported in patients who have used higher than recommended concentrations of lindane, or after a second application of lindane to the skin in the treatment of scabies and pediculosis: lindane should not be used as a first-line treatment in the management of the latter conditions. Babies, children, the elderly and people weighing less than 50 kg are considered to be particularly at risk. Lindane should not be used in patients who have a body-weight less than 50 kg, a history of epilepsy, have open or crusted sores on the skin around the head and neck or broken skin around the treatment areas, or skin conditions such as psoriasis or atopic dermatitis. Lindane is excreted into the breast milk but the amount excreted is not considered to be clinically significant; breastfeeding should, however, be avoided for at least 4 days after stopping treatment. There are limited human data on the use of lindane in pregnancy and *animal* data indicate a low risk for congenital defects, but because of its serious toxic potential safer alternative products are recommended.

Seizures have been reported after the topical use of lindane.[1] In reply, one of the manufacturers stated that up to the end of 1983 they were aware of 21 cases of convulsive disorders apparently associated with the use of their product; it had been used by over 40 million people. Of the 21 cases, the seizures were definitely or probably caused by the product in 11, but in 9 the seizures were associated with ingestion or excessive use.[2] From 1998 to 2003, 870 cases of unintentional lindane ingestion were reported in the USA.[3] Signs and symptoms of illness after ingestion included abdominal cramps, confusion, cough, headache, nausea, oral irritation, seizures, and vomiting.

Isolated reports of adverse effects associated with lindane include disseminated intravascular coagulation and subsequent death after oral ingestion[4] and aplastic anaemia after prolonged topical exposure (twice daily application for 3 weeks).[5]

1. Etherington JD. Major epileptic seizures and topical gammabenzene hexachloride. *BMJ* 1984; 289: 228.
2. Kelly VT. Major epileptic seizures and topical gammabenzene hexachloride. *BMJ* 1984; 289: 837.
3. CDC. Unintentional topical lindane ingestions—United States, 1998–2003. *MMWR* 2005; 54: 533–5. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5421a2.htm (accessed 22/04/08)
4. Rao CVSR, *et al.* Disseminated intravascular coagulation in a case of fatal lindane poisoning. *Vet Hum Toxicol* 1988; 30: 132–4.
5. Rauch AE, *et al.* Lindane (Kwell)-induced aplastic anemia. *Arch Intern Med* 1990; 150: 2393–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gamma-Scab; Hexa-Defital†; *Austria*: Jacutin†; *Braz.*: Pediletan; Pilensar†; *Canad.*: Hexit; *Chile*: Piomurol; *Hung.*: Jacutin†; *India*: Ascabiol; Bexarid; Gab; Gamaric; Gamascab; GBHC; Labscab; Nit-N-Mite†; Scaboma; *Indon.*: Obat Kutu Rambut Cap Dua Jempol†; *Israel*: Bicide†; *Malaysia*: Jacutin†; Scaboma; *Mex.*: Herklin; *NZ*: Benhex; *Pol.*: Jacutin†; *S.Afr.*: Gambex; *Singapore*: Jacutin; *Switz.*: Jacutin†; *Thai.*: Jacutin†; *Venez.*: Somergan.

Multi-ingredient Preparations. *Arg.*: Gamma-Scab; Hexa-Defital†; Lyndan; *Fr.*: Elenol†; *India*: Agloscab; Antiscab; Emscab†; Escab Plus; Freescab; Gamaley; Gamazex; GBTop; Novascab; NT-Scab; Scabine; Scaboma; Scarab; *Indon.*: Scabicid; Topicide†; *Mex.*: Herklin; *Singapore*: Jacutin.

Pharmacopoeial Preparations
USP 36: Lindane Cream; Lindane Lotion; Lindane Shampoo.

Lufenuron *(BAN, rINN)*

CGA-184699; Lufenurón; Lufénurone; Lufenuronum; Луфенурон.

1-[2,5-Dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-3-(2,6-difluorobenzoyl)urea; (*RS*)-*N*-[2,5-Dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenylcarbamoyl]-2,6-difluorobenzamide.

$C_{17}H_8Cl_2F_8N_2O_3$=511.1

CAS — 103055-07-8.

ATC Vet — QP53BC01.

UNII — 1R754M4918.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Lufenuron (Anhydrous) for Veterinary Use). A white or pale yellow powder. It exhibits polymorphism. Practically insoluble in water; soluble in anhydrous ethanol; freely soluble in acetonitrile.

Profile

Lufenuron is used as a systemic ectoparasiticide in veterinary practice; it is given orally (by adding to the feed) or by injection to the host animal.

Malathion *(BAN)*

Carbofos; Carbophos; Compound 4047; Malathionum; Malatión; Malation; Malationas; Malationi; OMS-1; Карбофос; Малатион.

Diethyl 2-(dimethoxyphosphinothioylthio)succinate.

$C_{10}H_{19}O_6PS_2$=330.3

CAS — 121-75-5.

ATC — P03AX03.

ATC Vet — QP53AF12.

UNII — U5N7SU872W.

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

Ph. Eur. 8: (Malathion). A clear, colourless or slightly yellowish liquid. It freezes at about 3 degrees. Slightly soluble in water; miscible with alcohol, with acetone, with cyclohexane, and with vegetable oils. Store in airtight containers. Protect from light.

USP 36: (Malathion). A clear, colourless, or slightly yellowish liquid with a characteristic odour. Congeals at about 2.9 degrees. Slightly soluble in water; miscible with alcohols, with ethers, with esters, with ketones, with aromatic and alkylated aromatic hydrocarbons, and with vegetable oils. Store in airtight containers. Protect from light.

Stability. The manufacturers have reported that malathion is sensitive to heat and is degraded at temperatures above 30 degrees.

Uses and Administration

Malathion is an organophosphorus insecticide (p. 2158.3). It is used in the treatment of head and pubic pediculosis (p. 2147.3) and in scabies (p. 2148.1); lotions of 0.5% and shampoos of 1% are commonly available. Lotions are generally preferred to shampoos as the contact time is longer. Aqueous lotions are preferred to treat pubic lice and scabies because alcoholic lotions are irritant to excoriated skin and the genitalia; aqueous lotions may also be preferable in asthmatic subjects or children to avoid alcoholic fumes. Skin or hair treated with an alcohol-based preparation should be allowed to dry naturally.

Malathion is also used in veterinary practice, agriculture, and horticulture. It is widely used for adult and larval mosquito control although resistance occurs.

Adverse Effects, Treatment, and Precautions

As for Organophosphorus Insecticides, p. 2158.3.

Malathion is one of the safer organophosphorus insecticides but its toxicity may be increased by the presence of impurities.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies malathion 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 26/10/11)

Toxicity. Acute renal insufficiency has been described in a patient associated with excessive exposure to a malathion spray.[1] The condition resolved without specific treatment. Renal toxicity had not previously been associated with organophosphorus pesticides. In a second case of acute poisoning,[2] due to ingestion of malathion, mild transient renal insufficiency and proteinuria with several other late complications including cardiac arrhythmias, pulmonary oedema, diffuse interstitial fibrosis, and muscle weakness due to peripheral neuropathy, were seen subsequent to recovery from the initial cholinergic toxicity.

1. Albright RK, *et al.* Malathion exposure associated with acute renal failure. *JAMA* 1983; 250: 2469.
2. Dive A, *et al.* Unusual manifestations after malathion poisoning. *Hum Exp Toxicol* 1994; 13: 271–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Prioderm; Radikal; *Denm.*: Prioderm; *Fin.*: Prioderm; *Fr.*: Prioderm; *Gr.*: Sicaril; Specifthir; Zitotox; *Hong Kong*: A-Lices; *Irl.*: Derbac-M; Prioderm†; Quellada M†; Suleo-M†; *Israel*: Prioderm; *Ital.*: Aftir Gel; *Malaysia*: A-Lices; *Neth.*: Prioderm; *Norw.*: Prioderm; *NZ*: A-Lices; Derbac-M; Prioderm†; *Philipp.*: A-Lices; *Rus.*: Pediilin (Педилин)†; *Singapore*: A-Lices; Derbac-M; Lice Care; *Swed.*: Prioderm; *Switz.*: Prioderm; *Thai.*: A-Lices; *UK*: Derbac-M; Prioderm†; Quellada M†; *Ukr.*: Pedilin (Педилин); *USA*: Ovide.

Multi-ingredient Preparations. *Arg.*: Para Plus; *Belg.*: Para Plus; *Fr.*: Para Plus; *Gr.*: Para-plus; *Israel*: Monocide†; Para Plus; *NZ*: Para Plus; *Rus.*: Para Plus (Пара Плюс); *Turk.*: Sac-Bi-Toks; *Ukr.*: Para Plus (Пара Плюс).

Pharmacopoeial Preparations
BP 2014: Malathion Lotion; Malathion Shampoo;
USP 36: Malathion Lotion.

Metaldehyde

Metaldehído; Метальдегид.

$(C_2H_4O)_4$

CAS — 9002-91-9.

Description. Metaldehyde is a cyclic polymer of acetaldehyde.

Uses

Metaldehyde is a molluscicide used in pellets against slugs and snails. It is an ingredient of some firelighters.

'Meta' is compressed metaldehyde which has been used as a solid fuel burning with a non-luminous carbon-free flame.

Adverse Effects and Treatment

Symptoms of poisoning by metaldehyde, which may be delayed, include vomiting and diarrhoea, fever, drowsiness, convulsions, and coma. Death from respiratory failure may occur within 48 hours. Kidney and liver damage may occur.

Treatment is symptomatic, although activated charcoal may be considered if more than 50 mg/kg has been ingested within the preceding hour.

References.
1. Longstreth WT, Pierson DJ. Metaldehyde poisoning from slug bait ingestion. *West J Med* 1982; 137: 134–7.
2. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners*. 2nd ed. London: DoH, The Stationery Office, 1996.
3. Bleakley C, *et al*. Self-poisoning with metaldehyde. *Emerg Med J* 2008; 25: 381–2.

Methomyl

Metomilo; Метомил.
S-Methyl *N*-(methylcarbamoyloxy)thioacetimidate.
$C_5H_{10}N_2O_2S$=162.2.
CAS — 16752-77-5.
UNII — 1NQ08HN025.

Profile

Methomyl is a carbamate insecticide (p. 2149.3) that has been used in agriculture.

References.
1. WHO. Methomyl health and safety guide. *IPCS Health and Safety Guide 97*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg097.htm (accessed 26/04/04)
2. WHO. Methomyl. *Environmental Health Criteria 178*. Geneva: WHO, 1996. Available at: http://www.inchem.org/documents/ehc/ehc/ehc178.htm (accessed 26/04/04)

Reports[1,2] of poisoning with methomyl and its management.

1. Martinez-Chuecos J, *et al*. Management of methomyl poisoning. *Hum Exp Toxicol* 1990; 9: 251–4.
2. Buchholz U, *et al*. An outbreak of food-borne illness associated with methomyl-contaminated salt. *JAMA* 2002; 288: 604–10.

Methoprene *(rINN)*

Methoprène; Methoprenum; Metopreno; ZR-515; Metonpeн.
Isopropyl 11-methoxy-3,7,11-trimethyldodeca-2(*E*),4(*E*)-dienoate.
$C_{19}H_{34}O_3$=310.5.
CAS — 40596-69-8.
ATC Vet — QP53AX28.
UNII — 88830OJ2UX.

Profile

Methoprene is an insect growth regulator which mimics the action of insect juvenile hormones and, if it is applied at the appropriate period of sensitivity, it causes death by preventing the transformation of larva to pupa. It is used against a variety of insects including fleas and mosquitoes. It is used in veterinary practice for the control of ectoparasites in the environment, rather than being applied to the animals themselves. It is also used in agriculture.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Altopou†.

Methoxychlor

Methoxy-DDT; Metoksychlor; Metoxicloro; Метоксихлор.
1,1,1-Trichloro-2,2-bis(*p*-methoxyphenyl)-ethane.
$C_{16}H_{15}Cl_3O_2$=345.6.
CAS — 72-43-5.
UNII — RIA79UD69L.

Profile

Methoxychlor is a chlorinated insecticide (p. 2150.2) used in agriculture, horticulture, and veterinary practice.

Methyl Bromide

Bromometano; Metilo, bromuro de; Monobromometano; Метилбромид.
Bromomethane; Monobromomethane.
CH_3Br=94.94.
CAS — 74-83-9.
UNII — 9V42E1Z7B6.

Uses

Methyl bromide has been used as an insecticidal fumigant for soil and some foodstuffs.

When supplied for fumigation it usually contains chloropicrin as a lachrymatory warning agent.

Methyl bromide has been used as a gaseous disinfectant; it has low antimicrobial activity but good penetrating power.

Methyl bromide was formerly used with carbon tetrachloride in some fire extinguishers. It has also been used as a refrigerant.

General references.
1. WHO. Methyl bromide (bromomethane) health and safety guide. *IPCS Health and Safety Guide 86*. Geneva: WHO, 1994. Available at: http://www.inchem.org/documents/hsg/hsg/hsg86_e.htm (accessed 26/04/04)
2. WHO. Methyl bromide. *Environmental Health Criteria 166*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc166.htm (accessed 26/04/04)

Adverse Effects, Treatment, and Precautions

Methyl bromide is a vesicant. Toxic effects after inhalation or percutaneous absorption are mainly due to neurotoxicity and include dizziness, headache, vomiting, blurred vision, weakness, ataxia, confusion, mania, hallucinations, mental depression, convulsions, pulmonary oedema, and coma. Renal and hepatic toxicity may also occur and death may be due to circulatory collapse or respiratory failure. Onset of symptoms may be preceded by a latent period. Concentrations of 1% or more are irritant to the eyes. Treatment is symptomatic although dimercaprol or acetylcysteine therapy has been tried.

Rubber absorbs and retains methyl bromide and should not therefore be used in protective clothing.

References[1-10] to toxicity of methyl bromide including reports of poisoning.

1. Chavez CT, *et al*. Methyl bromide optic atrophy. *Am J Ophthalmol* 1985; 99: 715–19.
2. Langard S, *et al*. Fatal accident resulting from methyl bromide poisoning after fumigation of a neighbouring house: leakage through sewage pipes. *J Appl Toxicol* 1996; 16: 445–8.
3. De Haro L, *et al*. Central and peripheral neurotoxic effects of chronic methyl bromide intoxication. *J Toxicol Clin Toxicol* 1997; 35: 29–34.
4. Michaiodimitrakis MN, *et al*. Death following intentional methyl bromide poisoning: toxicological data and literature review. *Vet Hum Toxicol* 1997; 39: 30–4.
5. Horowitz BZ, *et al*. An unusual exposure to methyl bromide leading to fatality. *J Toxicol Clin Toxicol* 1998; 36: 353–7.
6. Lifshitz M, Gavrilov V. Central nervous system toxicity and early peripheral neuropathy following dermal exposure to methyl bromide. *J Toxicol Clin Toxicol* 2000; 38: 799–801.
7. Yamano Y, *et al*. Three cases of acute methyl bromide poisoning in a seedling farm family. *Ind Health* 2001; 39: 353–6.
8. Hoizey G, *et al*. An unusual case of methyl bromide poisoning. *J Toxicol Clin Toxicol* 2002; 40: 817–21.
9. Geyer HL, *et al*. Methyl bromide intoxication causes reversible symmetric brainstem and cerebellar MRI lesions. *Neurology* 2005; 64: 1279–81.
10. Breeman W. Methylbromide intoxication: a clinical case study. *Adv Emerg Nurs J* 2009; 31: 153–60.

Naled

Bromchlophos; Нанед.
Dimethyl 1,2-dibromo-2,2-dichloroethyl phosphate.
$C_4H_7Br_2Cl_2O_4P$=380.8.
CAS — 300-76-5.
UNII — PAM1AI9KU1.

Profile

Naled is an organophosphorus insecticide used as a topical ectoparasiticide in veterinary practice.

Naphthalene

Naftaleno; Naphthalin; Нафталин.
$C_{10}H_8$=128.2.
CAS — 91-20-3.
UNII — 2166IN72UN.

Uses

Naphthalene has been used in lavatory deodorant discs and in mothballs. It has also been used as a soil fumigant.

Adverse Effects, Treatment, and Precautions

Ingestion of naphthalene can produce headache, nausea and vomiting, diarrhoea, profuse sweating, dysuria, coma, and convulsions. Less than one naphthalene mothball (200 to 500 mg) may cause haemolysis. Ingestion of 5 to 15 g is considered lethal for adults and a dose as low as 74 mg/kg has proved fatal. In children ingestion of 100 mg/kg is lethal. Doses as low as 2 g and 80 mg/kg ingested over 2 days have proved fatal in young children. Treatment is symptomatic; lavage may be considered if the patient presents within 1 hour of ingestion. The vapour is irritating to the eyes; chronic exposure has led to cataract formation. Haemolytic anaemia and haematuria leading to acute renal failure may occur particularly in persons with G6PD deficiency. Blood transfusions may be required.

Pregnancy. Haemolytic anaemia in a neonate has been attributed to inhalation of naphthalene by the mother during the twenty-eighth week of pregnancy.[1]

1. Athanasiou M, *et al*. Hemolytic anemia in a female newborn infant whose mother inhaled naphthalene before delivery. *J Pediatr* 1997; 130: 680–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Tartephedreel; *Ger*: Pulmo Bronchialcomplex.

Norbormide

McN-1025; Norbormida; Норбормид.
5-[α-Hydroxy-α-(2-pyridyl)benzyl]-7-[α-(2-pyridyl)benzylidene]-8,9,10-trinorborn-5-ene-2,3-dicarboximide.
$C_{33}H_{25}N_3O_3$=511.6.
CAS — 991-42-4.

Profile

Norbormide is a selective rodenticide effective against most species of *rats*, in which it produces extreme irreversible peripheral vasoconstriction. It is not very toxic to other rodents.

Organophosphorus Insecticides

Insecticidas organofosforados; Organofosforlu İnsektisitler.

Description. The organophosphorus or organophosphate insecticides may be esters, amides, or thiol derivatives of phosphoric, phosphonic, phosphorothioic, or phosphonothioic acids.

References.
1. WHO. Organophosphorus insecticides: a general introduction. *Environmental Health Criteria 63*. Geneva: WHO, 1986. Available at: http://www.inchem.org/documents/ehc/ehc/ehc63.htm (accessed 19/07/04)

Adverse Effects

Organophosphorus insecticides are potent cholinesterase inhibitors and can be very toxic. This inhibition results in both muscarinic and nicotinic effects with some central involvement.

Toxic effects may include abdominal cramps, nausea, vomiting, diarrhoea, pancreatitis, urinary incontinence, miosis or mydriasis, weakness, respiratory disturbance, lachrymation, increased salivation and sweating, bradycardia or tachycardia, hypotension or hypertension, cyanosis, muscular twitching, and convulsions. Some organophosphorus compounds cause delayed neuropathy. CNS symptoms include restlessness, anxiety, dizziness, confusion, coma, and depression of the respiratory or cardiovascular system. Patients may experience mental disturbances. Inhalation or external contact can cause local as well as systemic effects.

Repeated exposure may have a cumulative effect though the organophosphorus insecticides are, in contrast to the chlorinated insecticides, rapidly metabolised and excreted and are not appreciably stored in body tissues.

References[1-12] to the adverse effects and poisoning encountered with organophosphorus compounds such as insecticides (including sheepdips).

1. Minton NA, Murray VSG. A review of organophosphate poisoning. *Med Toxicol* 1988; 3: 350–75.
2. Karalliedde L, Senanayake N. Organophosphorus insecticide poisoning. *Br J Anaesth* 1989; 63: 736–50.
3. Öztürk MA, *et al*. Anticholinesterase poisoning in Turkey—clinical, laboratory and radiologic evaluation of 269 cases. *Hum Exp Toxicol* 1990; 9: 273–9.
4. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 24/07/08)
5. Casey P, Vale JA. Deaths from pesticide poisoning in England and Wales: 1945–1989. *Hum Exp Toxicol* 1994; 13: 95–101.
6. Eyer P. Neuropsychopathological changes by organophosphorus compounds—a review. *Hum Exp Toxicol* 1995; 14: 857–64.
7. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners*. 2nd ed. London: DoH, The Stationery Office, 1996.
8. Steenland K. Chronic neurological effects of organophosphate pesticides. *BMJ* 1996; 312: 1312–13.
9. Brown AA, Brix KA. Review of health consequences from high-, intermediate- and low-level exposure to organophosphorus nerve agents. *J Appl Toxicol* 1998; 18: 393–408.
10. Koksal N, *et al*. Organophosphate intoxication as a consequence of mouth-to-mouth breathing from an affected case. *Chest* 2002; 122: 740–1.
11. Roberts DM, Aaron CK. Management of acute organophosphorus pesticide poisoning. *BMJ* 2007; 334: 629–34.
12. Aardema H, *et al*. Organophosphorus pesticide poisoning: causes and developments. *Neth J Med* 2008; 66: 149–53.

Treatment of Adverse Effects

Rapid treatment for poisoning with organophosphorus insecticides is essential. Use of gastric lavage may be considered if a substantial amount has been ingested within 1 to 2 hours of presentation, unless the product s

formulated in a hydrocarbon solvent (as there is a high risk of fatal aspiration pneumonia). Contaminated clothing should be removed and the skin, including any areas contaminated by vomiting or hypersecretion, should receive copious and prolonged washing with soap and water. Contamination of the eye is treated by washing of the conjunctiva. The patient should be treated with atropine (see Poisoning, p. 1311.3) and either pralidoxime (p. 1571.2) or obidoxime (p. 1566.3) and symptomatic treatment should be instituted. Diazepam is sometimes given; it may be necessary to give it parenterally in moderate to severe poisoning to control muscle fasciculations and convulsions; oral dosage in mild poisoning may be helpful in relieving anxiety. The patient should be observed for signs of deterioration due to delayed absorption.

Paraquat

Parakuat; Паракват.
1,1′-Dimethyl-4,4′-bipyridyldiylium ion.
$C_{12}H_{14}N_2$=186.3.
CAS — 4685-14-7.
UNII — PLG39H7695.

Paraquat Dichloride

Paraquat, dicloruro de; Паракват Дихлорид.
$C_{12}H_{14}Cl_2N_2$=257.2.
CAS — 1910-42-5.
UNII — 2KZ83GS573.

Uses

Paraquat is a contact herbicide widely used as the dichloride in agriculture and horticulture. Liquid concentrates are supplied in the UK only to approved users.

Adverse Effects

Concentrated solutions of paraquat may cause irritation, inflammation, and possibly blistering of the skin, cracking and shedding of the nails, and delayed healing of cuts and wounds. It is not significantly absorbed from undamaged skin. A few fatalities have occurred after skin contact, but these appear to have been associated with prolonged contact and concentrated solutions.

Splashes in the eye cause severe inflammation, which may be delayed for 12 to 24 hours, corneal oedema, reduced visual acuity, and extensive superficial stripping of the corneal and conjunctival epithelium, which usually slowly heals. Inhalation of dust or spray may cause nasal bleeding.

Paraquat weedkillers available for use in domestic gardens contain 2.5% w/v paraquat, sometimes with other herbicides such as diquat. While this strength of paraquat can cause nausea and vomiting as well as some respiratory changes when ingested, it is not considered to be a lethal form.

Most of the cases of severe poisoning follow the ingestion or sometimes injection of the concentrated forms of paraquat herbicide (20% w/v), the distribution of which is restricted to agriculturalists and horticulturalists. Ingestion of, or dermal exposure to small amounts of concentrated paraquat may result in severe pulmonary fibrosis and death within 24 hours. A dose of 10 to 15 mL of the concentrate (20% w/v) is considered to be lethal. Most, but not all patients who ingest 20 to 40 mg of paraquat ion/kg (7.5 to 15 mL of the concentrate) die within 2 or 3 weeks after ingestion. Ingestion of doses of more than 40 mg of paraquat ion/kg (more than 15 mL of concentrate) usually results in death within 1 to 7 days after ingestion. The irritant effects of paraquat are reflected in oesophageal ulceration and gastrointestinal effects. There is widespread organ damage, most notably involving the kidneys and lungs. In such poisoning death is virtually certain and occurs rapidly.

Preparations of paraquat may contain an emetic or a laxative and some contain a malodorous agent to deter ingestion.

General references[1-9] concerning paraquat toxicity and its treatment.

1. WHO. Paraquat and diquat. *Environmental Health Criteria 39.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc39.htm (accessed 26/04/04)
2. Bismuth C, *et al.* Paraquat poisoning. *Drug Safety* 1990; 5: 243–51.
3. Pond SM. Manifestations and management of paraquat poisoning. *Med J Aust* 1990; 152: 256–9.
4. Paraquat health and safety guide. *Health and Safety Guide 51.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg051.htm (accessed 26/04/04)
5. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 21/07/08)
6. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners.* 2nd ed. London: DoH, The Stationery Office, 1996.
7. Biddleston M, *et al.* Prospects for treatment of paraquat-induced lung fibrosis with immunosuppressive drugs and the need for better prediction of outcome: a systematic review. *Q J Med* 2003; 96: 809–24.
8. Dinis-Oliveira RJ, *et al.* Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. *Crit Rev Toxicol* 2008; 38: 13–71.
9. Chen HW, *et al.* Intravenous paraquat poisoning. *J Chin Med Assoc* 2009; 72: 547–50.

Treatment of Adverse Effects

After contact with paraquat, contaminated clothing should be removed and the skin washed with soap and water. The eyes, if splashed, should be irrigated; later topical therapy may involve the symptomatic use of antibacterials or corticosteroids.

There is no specific treatment for paraquat poisoning and the immediate aim is to remove or inactivate the paraquat. Although the benefit of gastric decontamination is uncertain, if the patient presents less than 6 hours after ingestion the initial management involves giving an oral adsorbent, preferably activated charcoal in a dose of 100 g and followed by 50 g every 2 hours for up to 6 hours post ingestion. Fuller's earth and bentonite have been used as alternative oral adsorbents. When none of these adsorbents is available, a suspension of clay or of uncontaminated soil should be considered if medical attention is likely to be delayed. An osmotic laxative may be used with the first dose of the adsorbent in order to hasten bowel evacuation and prevent obstruction due to the adsorbent. Patients may require intensive supportive therapy, but oxygen should not be given initially as it appears to enhance the pulmonary toxicity of paraquat; however, it may be needed in later stages as part of palliative care.

Methods aimed at hastening elimination such as forced diuresis, peritoneal dialysis, haemodialysis, and haemoperfusion have been tried but the first three appear to be ineffective and results with the last method have varied; no method is of proven value.

For some general references concerning the treatment of paraquat toxicity, see under Adverse Effects, above.

Once paraquat has been absorbed, moderate to severe poisoning may result in acute renal failure, hepatitis, and pulmonary fibrosis; death may occur after 2 to 3 weeks. Pulse therapy with cyclophosphamide and methylprednisolone might be of benefit in such patients but not in those with fulminant poisoning.[1,2] Delayed management with such immunosuppressive regimens has been described;[3] however, use of sirolimus has proved unsuccessful in another case.[4]

1. Lin J-L, *et al.* Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat poisoning: a preliminary report. *Thorax* 1996; 51: 661–3.
2. Lin J-L, *et al.* A prospective clinical trial of pulse therapy with glucocorticoid and cyclophosphamide in moderate to severe paraquat poisoned patients. *Am J Respir Crit Care Med* 1999; 159: 357–60. Correction to the dose of cyclophosphamide. *ibid.* 2001; 163: 292.
3. Descatha A, *et al.* Delayed immunosuppressive treatment in life-threatening paraquat ingestion: a case report. *J Med Toxicol* 2009; 5: 76–9.
4. Lorenzen JM, *et al.* Failed rescue therapy with rapamycin after paraquat intoxication. *Clin Toxicol* 2010; 48: 84–6.

Parathion

Paration; Паратион.
O,O-Diethyl *O*-4-nitrophenyl phosphorothioate.
$C_{10}H_{14}NO_5PS$=291.3.
CAS — 56-38-2.
UNII — 61G466064D.

Profile

Parathion is an organophosphorus insecticide (p. 2158.3) that has been used in agriculture and horticulture. Its metabolite diethyl nitrophenyl phosphate (paraoxon) contributes to its toxicity.

References.

1. WHO. Parathion health and safety guide. *IPCS Health and Safety Guide 74.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/hsg/hsg/hsg74.htm (accessed 26/04/04)

Reports[1-7] of poisoning with parathion.

1. Anastassiades CJ, Ioannides M. Organophosphate poisoning and auricular fibrillation. *BMJ* 1984; 289: 290.
2. Golsousidis H, Kokkas V. Use of 19 590 mg of atropine during 24 days of treatment, after a case of unusually severe parathion poisoning. *Hum Toxicol* 1985; 4: 339–40.
3. Clifford NJ, Nies AS. Organophosphate poisoning from wearing a laundered uniform previously contaminated with parathion. *JAMA* 1989; 262: 3035–6.
4. Wang M-H, *et al.* Q-T interval prolongation and pleomorphic ventricular tachyarrhythmia ('Torsade de pointes') in organophosphate poisoning: report of a case. *Hum Exp Toxicol* 1998; 17: 587–90.
5. Eyer F, *et al.* Human parathion poisoning: a toxicokinetic analysis. *Toxicol Rev* 2003; 22: 143–63.
6. Lund CM, Iversen G. Bladanforgiftning forekommer endnu. *Ugeskr Laeger* 2005; 167: 3195–6.
7. Hoffmann U, Pappendorf T. Organophosphate poisonings with parathion and dimethoate. *Intensive Care Med* 2006; 32: 464–8.

Pentachlorophenol

PCP; Penta; Pentaclorofenol; Пентахлорфенол.
C_6HCl_5O=266.3.
CAS — 87-86-5.
UNII — D985U0SE4T.

NOTE. The name PCP has also been used as a synonym for phencyclidine hydrochloride (p. 2587.3).

Uses

Pentachlorophenol has been used mainly as the sodium salt (C_6Cl_5NaO = 288.3), as a preservative for a wide range of industrial and agricultural products, including wood and other building materials, textiles, glues, and starch. It has also been used for the control of slime and algae, and as a molluscicide, fungicide, and herbicide.

Adverse Effects, Treatment, and Precautions

Pentachlorophenol may be absorbed in toxic amounts through the skin or by inhalation, as well as by ingestion. Pentachlorophenol and its aqueous solutions are irritant to the eyes, mucous membranes, and to the skin, and may produce caustic burns. The systemic effects are due to uncoupling of oxidative phosphorylation with consequent stimulation of cellular metabolism. Acute poisoning with pentachlorophenol increases metabolic rate, leading to raised temperature with copious sweating and thirst, restlessness, fatigue, increased rate and depth of respiration, and tachycardia. There may be abdominal pain and nausea, and death has occurred from respiratory failure. Symptoms of subacute or chronic poisoning include hyperpyrexia and CNS, haematological, renal, reproductive, respiratory, and skin disorders.

Treatment is symptomatic. Raised body temperature should be treated by physical means; the use of antipyretics is not recommended since they can increase toxicity.

Reviews[1-5] of the toxicity of pentachlorophenol.

1. Health and Safety Executive. Pentachlorophenol. *Toxicity Review 5.* London: HMSO, 1982.
2. WHO. Pentachlorophenol. *Environmental Health Criteria 71.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc71.htm (accessed 26/04/04)
3. Pentachlorophenol health and safety guide. *Health and Safety Guide 19.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg019.htm (accessed 26/04/04)
4. Jorens PG, Schepens PJC. Human pentachlorophenol poisoning. *Hum Exp Toxicol* 1993; 12: 479–95.
5. Proudfoot AT. Pentachlorophenol poisoning. *Toxicol Rev* 2003; 22: 3–11.

There have been reports of malignant neoplasms,[1,2] aplastic anaemia,[3] pancreatitis,[4] intravascular haemolysis,[5] and urticaria[6] associated with exposure to pentachlorophenol.

1. Greene MH, *et al.* Familial and sporadic Hodgkin's disease associated with occupational wood exposure. *Lancet* 1978; ii: 626–7.
2. Hardell L. Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. *Lancet* 1979; i: 55–6.
3. Roberts HJ. Aplastic anemia due to pentachlorophenol. *N Engl J Med* 1981; 305: 1650–1.
4. Cooper RG, Macaulay MB. Pentachlorophenol pancreatitis. *Lancet* 1982; i: 517.
5. Hassan AB, *et al.* Intravascular haemolysis induced by pentachlorophenol. *BMJ* 1985; 291: 21–2.
6. Kentor PM. Urticaria from contact with pentachlorophenate. *JAMA* 1986; 256: 3350.

Pharmacokinetics

Pentachlorophenol may be absorbed after ingestion or inhalation or through the skin. After ingestion, the majority of a dose is eliminated in the urine as unchanged pentachlorophenol and its glucuronide, with small amounts appearing in the faeces.

Permethrin *(BAN, USAN, rINN)*

Perméthrine; Permethrinum; Permetriini; Permetrin; Permetrina; Permetryna; Перметрин.
3-Phenoxybenzyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{21}H_{20}Cl_2O_3$=391.3.
CAS — 52645-53-1.
ATC — P03AC04.
ATC Vet — QP53AC04.
UNII — 509F88P9SZ.

Profile

Permethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1). It is used in the treatment of head pediculosis (p. 2147.3) as a 1% application; there have been signs of resistance. It is also used as a 5% cream for pubic pediculosis (p. 2147.3) and as an acaricide in the treatment of scabies (p. 2148.1).

Permethrin is also used as a topical ectoparasiticide in veterinary practice and as an agricultural, horticultural, and household insecticide.

Permethrin is active against mosquitoes and is widely used for the impregnation of bednets and curtains in the control of malaria (p. 644.1). It is also active against blackflies in the adult and larval stages and is used for the

larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2). It is also active against tsetse flies.

Permethrin is suitable for aircraft disinsection.

References.

1. WHO. Permethrin health and safety guide. *IPCS Health and Safety Guide* 33. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg033.htm (accessed 26/04/04)
2. WHO. Permethrin. *Environmental Health Criteria 94*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc94.htm (accessed 26/04/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies permethrin 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 26/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Assy Crema de Enjuague; Assy Espuma; Assy Tratamiento Integral; B-Jen; Blum; Capitis; Dermoper; Pripi; Hairclin; Helpp; Kinderval; Kwell; Nopucid; Pedicrem; Pelo Libre; Quitoso NF; Witty; *Austral.*: Lyclear; Pyrifoam; Quellada; *Austria*: Infectoscab; *Belg.*: Mouskito Textile†; Nix; Zalvor; *Braz.*: Clean Hair; Keltrina; Kwell; Nedax Plus; Nedax; Pediletan Permetrina; Piodrex; Pioletal; Piosan; *Canad.*: Kwellada-P; Nix; *Chile*: Kilnits; Nolais; Cz.: Infectoscab; *Denm.*: Nix; *Fin.*: Nix; *Fr.*: Biovectrol Tissu; Cinq sur Cinq; Insect Ecran; Mousticologne†; Parapoux†; Pharmavoyage Moustiquaires; *Ger.*: InfectoPedicul; Infectoscab; *Gr.*: Nix; *Hong Kong*: A-Scabs; Quellada; *Hung.*: Infectoscab; *India*: Clearkin; Endlic; Jolice; Medilice; Merisoft; Metper; Mityscab; Monoscab; Perlice; Permite; *Indon.*: Scabimite; *Irl.*: Lyclear; *Israel*: Lyclear; Mite-X†; New-Nok; Zehu-Ze†; *Ital.*: Nix; Pre Clean Mom; Scabiadd; Scabianil; *Malaysia*: A-Scabs; *Mex.*: Novo-Herklin 2000; Scabisan Plus; Scabisan; *Neth.*: Loxazol; *Norw.*: Nix; *NZ*: Lyderm; Pyrifoam; *Philipp.*: Kwell Reformulated; Lindell; Pyrifoam; *Pol.*: Infectoscab; *Port.*: Nix; Quitoso; *Rus.*: Nittyfor (Ниттифор); Nix (Никс); *S.Afr.*: Lyclear; Skabi-Rid; *Spain*: Perme-Cure; Sarcop; *Swed.*: Nix; *Switz.*: Loxazol; *Turk.*: Anti-Scab; Kwellada; Niksen†; Zalvor; *UK*: Lyclear Creme Rinse; Residex P55; *Ukr.*: Nittyfor (Ниттифор); Permin (Пермин); *USA*: Acticin; Elimite; Nix; *Venez.*: Piokil Plus.

Multi-ingredient Preparations. *Arg.*: Bencil Scab; Detebencil Nit; Detebencil; Detebencil; Hexa-Defital Plus; Hexabencil; Kinderval Max; Para Plus; Perbel; Permecil; *Belg.*: Para Plus; Shampoux†; *Fr.*: Altopou†; Charlieu Anti-Poux†; Para Plus; Pyreflor†; Pyreflor; *Gr.*: Para-plus; *India*: Escab Plus; *Israel*: Para Plus; *Ital.*: Antiscabbia CM; *NZ*: Active Duty with Sunscreen; Active Duty; Para Plus; *Rus.*: Para Plus (Пара Плюс); *S.Afr.*: Nitagon; *Ukr.*: Para Plus (Пара Плюс).

Phenothrin *(BAN, rINN)*

Fenotrin; Fenotrina; Phénothrine; Phenothrinum; S-2539; Фенотрин.

3-Phenoxybenzyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

$C_{23}H_{26}O_3$=350.5

CAS — 26002-80-2.

ATC — P03AC03.

ATC Vet — QP53AC03.

UNII — 707484X33X.

Profile

Phenothrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1). It is used for the treatment of head and pubic pediculosis (p. 2147.3) as a 0.2% alcoholic or 0.5% aqueous lotion, or as a 0.5% alcoholic foam; as with permethrin there have been signs of resistance.

Phenothrin is also used in veterinary practice as a topical ectoparasiticide, as a household insecticide, and for the disinsection of public areas and aircraft.

References.

1. WHO. d-Phenothrin health and safety guide. *IPCS Health and Safety Guide* 32. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg032.htm (accessed 26/04/04)
2. WHO. d-Phenothrin. *Environmental Health Criteria 96*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc96.htm (accessed 26/04/04)

Aircraft disinsection. References.

1. Russell RC, Paton R. In-flight disinsection as an efficacious procedure for preventing international transport of insects of public health importance. *Bull WHO* 1989; 67: 543–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nopucid MC; Sumo; *Cz.*: Parasidose; *Fr.*: Itax Antipoux; Item Antipoux; Parasidose; *Gr.*: Ivaliten; Pubex; Sitem; Venatren; *Irl.*: Full Marks†; Headmaster†; *Israel*: Sof-Sof†; *Ital.*: Cruzzy Shampoo Potenziato alla Sumitrina; Mediker; Mom Gel; Mom Shampoo Schiuma; Neo Mom; Ottocid; *Mex.*: Herklin NP; *Mon.*: Hegor; *NZ*: Full Marks; Parasidose; *Port.*: Parasidose; *Rus.*: Anti-Bit (Анти-Вит)†; Itax (Итакс); Parasidose (ПараэИДОЗ); *Turk.*: Anti-Bit; *UK*: Full Marks†; *USA*: Pronto.

Multi-ingredient Preparations. *Fr.*: A-Par; *Gr.*: Cif Candioli; *Ital.*: Neo Mom; *Mex.*: Herklin NF.

Phosmet *(BAN)*

Fosmet; Фталофос; Фосмет.

O,O-Dimethyl phthalimidomethyl phosphorodithioate.

$C_{11}H_{12}NO_4PS_2$=317.3

CAS — 732-11-6.

ATC Vet — QP53AF06; QP53BB03.

UNII — VN04LI540Y.

Profile

Phosmet is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal. It has also been used in agriculture and horticulture.

Phoxim *(BAN, pINN)*

Bayer-9053; Foksiimi; Foxim; Foxima; Phoxime; Phoximum; Фоксим.

2-(Diethoxyphosphinothioyloxyimino)-2-phenylacetonitrile.

$C_{12}H_{15}N_2O_3PS$=298.3

CAS — 14816-18-3.

ATC Vet — QP53AF01.

UNII — 6F5V775VPO.

Profile

Phoxim is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice. It is also used for the larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2).

Piperonal

Heliotropin; Heliotropina; Piperonylaldehyde; Пиперонал.

1,3-Benzodioxole-5-carboxaldehyde.

$C_8H_6O_3$=150.1

CAS — 120-57-0.

UNII — KE109YAK00.

Profile

Piperonal is used as an insect repellent against head lice (see Pediculosis, p. 2147.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Rappell.

Piperonyl Butoxide *(BAN)*

Piperonil Butoksit; Piperonilo, butóxido de; Пиперонилбутоксил.

5-[2-(2-Butoxyethoxy)ethoxymethyl]-6-propyl-1,3-benzodioxole.

$C_{19}H_{30}O_5$=338.4

CAS — 51-03-6.

UNII — LWK91TU9AH.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Piperonyl Butoxide). A yellow or pale brown oily liquid. Very slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with petroleum oils.

Profile

Piperonyl butoxide is used as a synergist for pyrethrin and pyrethroid insecticides. Mixtures of piperonyl butoxide and pyrethrins or pyrethroids are used in the treatment of pediculosis (p. 2147.3).

Piperonyl butoxide is considered to cause a variety of gastrointestinal effects as well as mild CNS depression.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Deca-Scab; Hexa-Defital NF; Limpacid; Nopucid Compuesto; Nopucid Rapida; Para Piojicida; Para Plus; Scabioderm; *Austral.*: Banlice; Paralice; *Belg.*: Para Plus; Para; Shampoux†; *Braz.*: Deltacid Plus; *Canad.*: Lice Killing; Pronto; R & C†; R & C; *Chile*: Launol; *Fr.*: Altopou†; Charlieu Anti-Poux†; Para Plus; Para Special Poux; Pyreflor†; Pyreflor; Spray-Pax; Spregal; *Ger.*: Goldgeist; Jacutin; Spregal†; *Gr.*: Lice-Enz; Mom; Para-plus; Runde; Spregal; *Israel*: Acardus; Kin Soff†; Para Plus; *Ital.*: Baygon; Cruzzy; Milice; Sinezar; *Neth.*: Para-Speciaal†; Spregal; *NZ*: Para Plus; *Rus.*: Para Plus (Пара Плюс); Pedilin Ко (Педилин Ко)†; Spray-Pax (Спрей-пакс); Spregal (Спрегаль); *S.Afr.*: Nitagon; Spregal; *Turk.*: Kwell-P; *UK*: Fortefog; Prevent; *Ukr.*: Para Plus (Пара Плюс); Pedilin Ко (Педилин Ко)†; Spray-Pax (Спрей-Пакс)†; Spregal (Спрегаль); *USA*: Blue; Licide; Pronto; Pyrinyl II; Pyrinyl Plus; RID; Tisit.

Pirimiphos-Methyl

Metilpirimifós; Pyrimiphos Methyl; Пиримифос-метил.

O-2-Diethylamino-6-methylpyrimidin-4-yl *O,O*-dimethyl phosphorothioate.

$C_{11}H_{20}N_3O_3PS$=305.3

CAS — 29232-93-7.

UNII — 2VQZ4PK548.

Profile

Pirimiphos-methyl is an organophosphorus insecticide (p. 2158.3). It is used in agriculture and domestically.

Propetamphos *(BAN)*

Propetamfos; Propetamfós; Пропетамфос.

Isopropyl (*E*)-3-[(ethylamino)(methoxy)phosphinothio-oxy but-2-enoate.

$C_{10}H_{20}NO_4PS$=281.3

CAS — 31218-83-4.

ATC Vet — QP53AF09.

UNII — G4A07F635U.

Profile

Propetamphos is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice.

Propoxur *(BAN)*

Пропоксур.

2-Isopropoxyphenyl methylcarbamate.

$C_{11}H_{15}NO_3$=209.2

CAS — 114-26-1.

ATC Vet — QP53AE02.

UNII — BFH029TL73.

Profile

Propoxur is a carbamate insecticide (p. 2149.3) used as a topical ectoparasiticide in veterinary practice. It is also used as a fumigant in agriculture.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Pyraclofos

Piraclofós; Пираклофос.

(*RS*)-[O-1-(4-Chlorophenyl)pyrazol-4-yl *O*-ethyl *S*-propyl phosphorothioate].

$C_{14}H_{18}ClN_2O_3PS$=360.8

CAS — 77458-01-6.

Profile

Pyraclofos is an organophosphorus insecticide (p. 2158.3) used for the larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2).

Pyraclostrobin

Пираклостробин.

Methyl 2-[1-(4-chlorophenyl)pyrazol-3-yloxymethyl]-*N*-methoxycarbanilate.

$C_{19}H_{18}ClN_3O_4$=387.8

CAS — 175013-18-0.

UNII — DJW8M9OX1H.

Profile

Pyraclostrobin is a fungicide used for the treatment and control of fungal plant disease.

Pyrethrum Flower

Chrysanthème Insecticide; Dalmatian Insect Flowers; Flor del pelitre; Flor del Piretro; Insect Flowers; Insektenblüten; Piretro; Pyrethri Flos; Цветки Ромашки Далматской.
CAS — 8003-34-7 (pyrethrum); 121-21-1 (pyrethrin I); 121-29-9 (pyrethrin II); 25402-06-6 (cinerin I); 121-20-0 (cinerin II).
ATC — P03AC01.
ATC Vet — QP53AC01.
ATC Herb — HP03AC500? (Tanacetum cinerariifolium: flower); HP03BA500? (Tanacetum cinerariifolium: flower).
UNII — CGF76TP7X6 (Tanacetum cinerariifolium); ZUM06L90GV (pyrethrum extract).

Pharmacopoeias. In *BP(Vet)*, which also includes the extract.

US includes only the extract.

BP(Vet) 2014: (Pyrethrum Flower). The dried flowerheads of *Chrysanthemum cinerariaefolium* containing not less than 1% of pyrethrins of which not less than one-half consists of pyrethrin I. It has a faint but characteristic odour.

BP(Vet) 2014: (Pyrethrum Extract). An extract prepared from Pyrethrum Flower. It contains 24.5 to 25.5% of pyrethrins, of which not less than half consists of pyrethrin I. A dark olive green or brown viscous liquid or, if decolourised, a pale amber liquid. Store in a well-filled container. Protect from light. It should be thoroughly stirred before use.

USP 36: (Pyrethrum Extract). A mixture of three naturally occurring, closely related insecticidal esters of chrysanthemic acid (pyrethrins I: jasmolin I, cinerin I, and pyrethrin I) and three closely related esters of pyrethric acid (pyrethrins II: jasmolin II, cinerin II, and pyrethrin II). The ratio of pyrethrins I to pyrethrins II is not less than 0.8 and not more than 2.8. It may contain pigments characteristic of chrysanthemum species, triglyceride oils, terpenoids, and carotenoid. It may also contain suitable solvents and antoxidants. It contains no other added substances. It is a pale yellow liquid having a bland, flowery odour. Insoluble in water; soluble in liquid paraffin and in most organic solvents. Store in airtight containers. Protect from light.

Uses

Pyrethrum flower is mainly used for the preparation of pyrethrum extracts containing a mixture of chrysanthemic acid and pyrethric acid esters (pyrethrins I and II).

Pyrethrins in the form of pyrethrum extract have a long history of use as insecticides. Pyrethrum is rapidly toxic to many insects. It has a much quicker knock-down effect than clofenotane or lindane, but it is less persistent and less stable. Its action can be enhanced by certain substances such as piperonyl butoxide (p. 2160.2), and pyrethrins with piperonyl butoxide are used clinically in the treatment of pediculosis (p. 2147.3).

Pyrethroid insecticides (synthetic analogues of pyrethrins), such as permethrin and phenothrin, are also used clinically; deltamethrin and permethrin are among those used for the vector control of malaria.

Pyrethrum, pyrethrins, and pyrethroids are used as topical ectoparasiticides in veterinary practice and as agricultural, horticultural, and household insecticides. They are also used in total release foggers (or "bug bombs"); pesticide products that release their contents at once to fumigate an area.

Adverse Effects and Precautions

Pyrethrum is irritant to the eyes and mucosa. Hypersensitivity reactions have been reported.

References[1-6] to the potential for toxicity of pyrethrin and pyrethroid insecticides.

1. Ray DE, Forshaw PJ. Pyrethroid insecticides: poisoning syndromes, synergies, and therapy. *J Toxicol Clin Toxicol* 2000; **38**: 95–101.
2. Bateman DN. Management of pyrethroid exposure. *J Toxicol Clin Toxicol* 2000; **38**: 107–9.
3. Bradberry SM, *et al.* Poisoning due to pyrethroids. *Toxicol Rev* 2005; **24**: 93–106.
4. Proudfoot AT. Poisoning due to pyrethrins. *Toxicol Rev* 2005; **24**: 107–13.
5. Ray DE, Fry JR. A reassessment of the neurotoxicity of pyrethroid insecticides. *Pharmacol Ther* 2006; **111**: 174–93.
6. CDC. Illnesses and injuries related to total release foggers—eight states, 2001-2006. *MMWR* 2008; **57**: 1125–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Pearsol; SH3; *Philipp.*: Licealiz.

Multi-ingredient Preparations. *Austral.*: Banlice; *Canad.*: Lice Killing; Pronto; R & C†; R & C; *Fr.*: Spray-Pax; *Ger.*: Goldgeist; *Gr.*: Lice-Enz; *Israel*: Kin Soff†; *Ital.*: Milice; Sinezan; *Rus.*: Bubil (Бубил)†; Spray-Pax (Спрей-пакс); *Turk.*: Kwell-P; *UK*: Fortefog; Prevent; *Ukr.*: Spray-Pax (Спрей-Пакс)†; *USA*: Blue; Licide; Pronto; Pyrinyl II; Pyrinyl Plus; RID; Tisit.

Pyriproxyfen

Piriproxifeno; Pyriproksifeeni; Pyriproxifen; Pyriproxifène; Pyriproxifenum; Pyriproxyfeno; Pyriproxyfenum; S-9318; Sumilarv; 31183; Пирипроксифен.
2-[1-Methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine.
$C_{20}H_{19}NO_3$=321.4
CAS — 95737-68-1.
ATC Vet — QP53AX23.

Profile

Pyriproxyfen is used as a topical ectoparasiticide in veterinary practice.

Red Squill

Escila; Esquila; Морской Лук.
CAS — 507-60-8 (scilliroside).

Profile

Red squill is a red variety of *Urginea maritima*, which contains, in addition to cardiac glycosides, an active principle, scilliroside. It is very toxic to *rats* and has been incorporated in rat poisons; it has neurotoxic and cardiotoxic properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; *Ger.*: Asthmakhell N; Cardioject; *Neth.*: Asakell.

Resmethrin

Resmetrina; Ресметрин.
5-Benzyl-3-furylmethyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.
$C_{22}H_{26}O_3$=338.4
CAS — 10453-86-8.

Profile

Resmethrin is a pyrethroid insecticide (see Pyrethrum Flower, above) used in veterinary practice for the control of ectoparasites in the environment. Resmethrin is also used as an agricultural, horticultural, and household insecticide, but is not synergised by pyrethrum synergists such as piperonyl butoxide (p. 2160.2).

References.

1. WHO. Resmethrins. *Environmental Health Criteria 92*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc092.htm (accessed 26/04/04)
2. WHO. Resmethrins health and safety guide. *IPCS Health and Safety Guide 25*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg025.htm (accessed 26/04/04)

Rotenone

Rotenona; Rotenonum; Ротенон.
(2*R*,6a*S*,12a*S*)-1,2,6,6a,12,12a-Hexahydro-2-isopropenyl-8,9-dimethoxychromeno[3,4-*b*]furo[2,3-*h*]chromen-6-one.
$C_{23}H_{22}O_6$=394.4
CAS — 83-79-4.
UNII — 03L9OT429T.

Profile

Rotenone is a non-systemic insecticide used in agriculture and in horticulture.

Rotenone is the active ingredient of derris (the dried rhizome and roots of *Derris elliptica*; also known as tuba root or aker-tuba) and of lonchocarpus (the dried root of *Lonchocarpus utilis*; also known as cube root, timbo, or barbusco). Powdered forms of derris and of lonchocarpus have been used as insecticides and fish poisons.

References.

1. WHO. Rotenone health and safety guide. *IPCS Health and Safety Guide 73*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/hsg/hsg/hsg073.htm (accessed 26/04/04)

Sodium Fluoroacetate

Compound 1080; Fluoroacetato sódico; Sodium Monofluoroacetate; Фторацетат Натрия.
FCH_2CO_2Na=100.0
CAS — 62-74-8.
UNII — 166WTM3843.

Uses

Sodium fluoroacetate is a highly effective rodenticide but must be used with great caution because of its toxicity to other animals and to man.

Adverse Effects, Treatment, and Precautions

Sodium fluoroacetate is highly toxic, the lethal dose if ingested being about 1 to 5 mg/kg. Toxic effects may be delayed for several hours after oral absorption or inhalation, and include nausea and vomiting, apprehension, muscle twitching, cardiac irregularities, convulsions, respiratory failure, coma, and death usually due to ventricular fibrillation.

Treatment is generally supportive and symptomatic.

References[1-4] to sodium fluoroacetate toxicity.

1. Chi CH, *et al.* Clinical presentation and prognostic factors in sodium monofluoroacetate intoxication. *J Toxicol Clin Toxicol* 1996; **34**: 707–12.
2. Chi CH, *et al.* Hemodynamic abnormalities in sodium monofluoroacetate intoxication. *Hum Exp Toxicol* 1999; **18**: 351–3.
3. Goncharov NV, *et al.* Toxicology of fluoroacetate: a review, with possible directions for therapy research. *J Appl Toxicol* 2006; **26**: 148–61.
4. Proudfoot AT, *et al.* Sodium fluoroacetate poisoning. *Toxicol Rev* 2006; **25**: 213–19.

Spinosad *(USAN)*

LY-232105; PP-105; XDE-105.
CAS — 168316-95-8.
UNII — XPA88EAP6V.

Description. Spinosad is derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. It is a mixture of spinosad factor A (below) and spinosad factor D (below), in a ratio of about 5 to 1, respectively.

Spinosad Factor A

A-83543A; Lepicidin A; Spinosyn A.
(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-[(6-Deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyl)oxy]-13-[[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methyl-2*H*-pyran-2-yl]oxy]-9-ethyl-14-methyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecin-7,15-dione.
$C_{41}H_{65}NO_{10}$=732.0
CAS — 131929-60-7.
UNII — OY0L59V61N.

Spinosad Factor D

Spinosyn D.
(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-[(6-Deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyl)oxy]-13-[[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methyl-2*H*-pyran-2-yl]oxy]-9-ethyl-4,14-dimethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecin-7,15-dione.
$C_{42}H_{67}NO_{10}$=746.0
CAS — 131929-63-0.
UNII — 78G4631RTT.

Profile

Spinosad is an insecticide available as a 0.9% topical solution for the treatment of head pediculosis (p. 2147.3) in adults and children from 4 years of age. It should be applied to dry hair and left on for 10 minutes before rinsing out. Spinosad has ovicidal activity and therefore nit combing is not necessary; a second application is only required if live lice are seen 7 days after the first treatment. The solution contains benzyl alcohol which may cause fatal 'gasping syndrome' in neonates (see p. 1740.1).

It is also used as an agricultural and horticultural insecticide.

References.

1. Cole SW, Lundquist LM. Spinosad for treatment of head lice infestation. *Ann Pharmacother* 2011; **45**: 954–9.
2. McCormack PL. Spinosad: in pediculosis capitis. *Am J Clin Dermatol* 2011; **12**: 349–53.
3. Villegas SC, Breitzka RL. Head lice and the use of spinosad. *Clin Ther* 2012; **34**: 14–23.
4. Villegas SC. Spinosad for the treatment of head lice infestations. *Drugs Today* 2012; **48**: 595–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Natroba.

Sulfiram *(BAN, rINN)*

Monosulfiram; Sulfiramum; Сульфирам.
Tetraethylthiuram monosulphide.
$C_{10}H_{20}N_2S_3$=264.5
CAS — 95-05-6.
ATC Vet — QS02QA02.
UNII — IXHL4Q8P7Y.

Uses and Administration

Sulfiram is a pesticide that has been used as an acaricide, either alone or with benzyl benzoate, in the treatment of scabies (p. 2148.1), although other treatments are now preferred.

Sulfiram has also been used as a pesticide in veterinary practice.

Adverse Effects and Precautions

An erythematous rash has occasionally been reported. Sulfiram produces effects similar to those of disulfiram (p. 2496.1) if ingested with alcohol. As there may be a risk of absorption after application of sulfiram to the whole body, patients are advised to abstain from alcohol for at least 48 hours.

The reactions to alcohol occasionally reported in patients who have applied sulfiram solution[1,2] resemble those seen with disulfiram. Analysis has shown that sulfiram solutions exposed to room light undergo photochemical conversion to disulfiram, and that the concentration of disulfiram, and the ability of the solution to inhibit aldehyde dehydrogenase and hence the metabolism of alcohol, increases with the duration of such storage.[3,4] Whether patients who have applied sulfiram solution should avoid direct light immediately afterwards has not been elucidated.[4]

1. Blanc D, Deprez P. Unusual adverse reaction to an acaricide. *Lancet* 1990; 335: 1291–2.
2. Burgess L. Adverse reactions to monosulfiram. *Lancet* 1990; 336: 873.
3. Mays DC, *et al.* Photolysis of monosulfiram: a mechanism for its disulfiram-like reaction. *Clin Pharmacol Ther* 1994; 55: 191.
4. Lipsky JJ, *et al.* Monosulfiram, disulfiram, and light. *Lancet* 1994; 343: 304.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Sarfiram; Sulfitrat; Tetmosol; Valfiran; *India*: Cure Scab; Tetmosol; *S.Afr.*: Tetmosol.

Multi-ingredient Preparations. *Fr.*: Ascabiol.

Temefos *(USAN, rINN)*

27165; Temefós; Téméfos; Temefosum; Temephos; Темефос.

O,O'-(Thiodi-*p*-phenylene) *O,O,O',O'*-tetramethyl bis(phosphorothioate).

$C_{16}H_{20}O_6P_2S_3$=466.5

CAS — 3383-96-8.

UNII — ONP3ME32DL.

Profile

Temefos is an organophosphorus insecticide (p. 2158.3). It is effective against the larvae of mosquitoes, blackflies, and other insects, and is used for the larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2). It is also effective against the crustacean host to the larvae of the guinea worm and is used in the control of dracunculiasis (p. 145.1); treatment of drinking water is both effective and acceptable. It is also used as a topical ectoparasiticide in veterinary practice.

Tetrachlorvinphos

ENT-25841; SD-8447; Tetrachlorowinfos; Tetraclorvinfós; Тетрахлорвинфос.

2-Chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate.

$C_{10}H_9Cl_4O_4P$=366.0

CAS — 961-11-5; 22248-79-9 (Z-tetrachlorvinphos); 22350-76-1 (E-tetrachlorvinphos).

ATC Vet — QP53AF14.

Profile

Tetrachlorvinphos is an organophosphorus insecticide (p. 2158.3) used as an ectoparasiticide in veterinary practice.

Tetramethrin *(rINN)*

Tétraméthrine; Tetramethrinum; Tetrametrina; Тетраметрин.

Cyclohex-1-ene-1,2-dicarboximidomethyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

$C_{19}H_{25}NO_4$=331.4

CAS — 7696-12-0.

ATC — P03BA04.

ATC Vet — QP53AC13.

UNII — Z72930Q46K.

Profile

Tetramethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in the treatment of pediculosis (p. 2147.3). It is also used in veterinary practice for the control of ectoparasites in the environment and as a household insecticide.

References.

1. WHO. Tetramethrin health and safety guide. *IPCS Health and Safety Guide 31.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg031.htm (accessed 26/04/04)
2. WHO. Tetramethrin. *Environmental Health Criteria 98.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc98.htm (accessed 26/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: A-Par; *Gr.*: Cif Candioli; Mom; Runde; *Ital.*: Baygon; Neo Mom; *Rus.*: Pedilin Ko (Педилин Ко)†; *Ukr.*: Pedilin Ko (Педилин Ко)†.

Trichlorophenoxyacetic Acid

2,4,5-T; Triclorofenoxiacético, ácido; Трихлорфеноксиуксусная Кислота.

2,4,5-Trichlorophenoxyacetic acid.

$C_8H_5Cl_3O_3$=255.5

CAS — 35915-18-5.

UNII — 9Q963S4YMX.

Profile

Trichlorophenoxyacetic acid is a selective herbicide with similar actions to dichlorophenoxyacetic acid (p. 2152.2). It is usually used in ester formulations. It was used with dichlorophenoxyacetic acid as a defoliating agent in the Vietnam war.

Toxicity. The phenoxy herbicides were used for defoliation in Vietnam as Agent Orange, which consisted of a mixture of dichlorophenoxyacetic acid, trichlorophenoxyacetic acid, and the impurity TCDD (dioxin), and concern has been expressed that they may have contributed to an increased incidence of cancer among exposed subjects as well as an adverse effect on the offspring of those subjects. This has been a matter of considerable debate,[1] prompting a series of biennial reassessments of the health effects of Agent Orange by the US National Academy of Science's Institute of Medicine.[2] To date the Institute has concluded[3] that there is evidence of increased incidence of chronic lymphocytic leukaemia, soft tissue sarcoma, Hodgkin's disease, non-Hodgkin's lymphoma, and chloracne, with phenoxy herbicides.

1. McCarthy M. Agent Orange. *Lancet* 1993; 342: 362.
2. Stephenson J. New IOM report links Agent Orange exposure to risk of birth defect in Vietnam vets' children. *JAMA* 1996; 275: 1066–7.
3. Institute of Medicine. *Veterans and Agent Orange: update 2002 (200.* Washington: The National Academies Press. Also available at: http://www.nap.edu/openbook.php?isbn=0309086167 (accessed 24/07/08)

Triflumuron

Triflumurón; Trifluron; Трифлумурон.

2-Chloro-*N*-{[4-(trifluoromethoxy)phenyl]amino}carbonyl benzamide.

$C_{15}H_{10}ClF_3N_2O_3$=358.7

CAS — 64628-44-0.

UNII — 3FT64DYG8K.

Profile

Triflumuron is an insecticide used in agriculture and as a topical ectoparasiticide in veterinary practice.

Pharmaceutical Excipients

Binders and compression aids, p. 2163
Coatings and films, p. 2163
Colouring agents, p. 2163
Diluents and vehicles, p. 2163
Disintegrants, p. 2163
Emulsifying and solubilising agents, p. 2164
Flavours and sweeteners, p. 2164
Glidants and lubricants, p. 2165
Plasticisers, p. 2165
Preservatives, p. 2165
Propellants, p. 2165
Solvents, p. 2165
Stabilisers, p. 2166
Suspending agents and viscosity enhancers, p. 2166

Pharmaceutical excipients are substances that are included in a pharmaceutical dosage form not for their direct therapeutic action but to aid the manufacturing process; to protect, support, or enhance stability, bioavailability, or patient acceptability; to assist in product identification; or to enhance in another way the overall safety or function of the product during storage or use.

Although very diverse, excipients can be broadly classified according to their function or uses, and their chemical characteristics. Many excipients have more than one use (multifunctional excipients) and this can be an advantage since it reduces the number of excipients needed and minimises the risk of interactions between them.

Ideally, an excipient has no pharmacological action of its own, is non-toxic, and does not interact chemically or physically with the active ingredients or other excipients; however, few excipients meet these criteria in practice. Toxicity may relate to compounds used as excipients in the final dosage form, or to residues of compounds (such as solvents) used during the manufacturing process.

Basic details of the major groups of pharmaceutical excipients follow, together with lists of the substances described in this chapter.

General references.

1. Kalász H, Antal I. Drug excipients. *Curr Med Chem* 2006; 13: 2535–63.
2. Anonymous. What are excipients doing in medicinal products? *Drug Ther Bull* 2009; 47: 81–4.

Binders and compression aids

Binders, compression aids, and granulating agents are used in tablet and granule manufacture to hold the ingredients together and give the finished product mechanical strength. They are mainly natural or synthetic polymers, such as starches, sugars, and sugar alcohols (all of which are described in the chapter on Nutritional Agents, p. 2042.1), or cellulose derivatives. Gelatin (p. 1154.1), guar gum (p. 475.1), magnesium carbonate (p. 1856.2), and derivatives and polymers of methylmethacrylate (p. 2558.2) are also used.

Described in this chapter are

- Acacia, p. 2166.1
- Alginic Acid, p. 2167.2
- Aluminium Magnesium Silicate, p. 2168.2
- Carbomers, p. 2173.3
- Carmellose, p. 2175.1
- Cellulose, p. 2177.1
- Dextrates, p. 2181.1
- Ethylcellulose, p. 2185.2
- Glyceryl Behenate, p. 2186.2
- Hyetellose, p. 2188.3
- Hyprolose, p. 2189.1
- Hypromellose, p. 2189.2
- Methylcellulose, p. 2197.3
- Palm Oil, p. 2200.2
- Poloxamers, p. 2201.3
- Polydextrose, p. 2202.2
- Polyethylene Oxide, p. 2202.2
- Povidone, p. 2204.3
- Zein, p. 2221.2

Coatings and films

Tablets are usually coated to provide protection from the environment (air, light, and moisture), to increase mechanical strength, to mask taste and smell, to aid swallowing, and for product identification; coatings may also be used to modify the release of the active ingredient. Traditionally, sugar (sucrose, p. 2096.3) has been the most widely used coating; sealants such as cellulose or shellac, and subcoatings of acacia or gelatin (p. 1154.1) may be applied first, and waxes and paraffins may be used as a final polishing layer. However, this process has now mainly been replaced by film coating using natural or synthetic polymers such as cellulose derivatives, derivatives of methylmethacrylate (p. 2558.2), polyvinyl acetates, and shellac. Polymers that are insoluble in acid, such as phthalate derivatives, are used for enteric coatings. Other excipients used as coatings include glycerides of fatty acids, such as glyceryl behenate and glyceryl palmitostearate.

Described in this chapter are

- Beeswax, p. 2170.2
- Carmellose, p. 2175.1
- Carnauba Wax, p. 2176.2
- Cellaburate, p. 2177.2
- Cellacefate, p. 2177.3
- Cellulose Acetate, p. 2177.3
- Cetyl Alcohol, p. 2178.2
- Cetyl Esters, p. 2178.2
- Ethylcellulose, p. 2185.2
- Glyceryl Behenate, p. 2186.2
- Glyceryl Palmitostearate, p. 2187.2
- Hard Paraffin, p. 2188.1
- Hyetellose, p. 2188.3
- Hyprolose, p. 2189.1
- Hypromellose, p. 2189.2
- Macrogol Poly(vinyl Alcohol) Grafted Copolymer, p. 2194.3
- Methylcellulose, p. 2197.3
- Microcrystalline Wax, p. 2198.1
- Palm Oil, p. 2200.2
- Poloxamers, p. 2201.3
- Polyvinyl Acetate, p. 2204.1
- Povidone, p. 2204.3
- Pullulan, p. 2206.3
- Shellac, p. 2208.3
- Zein, p. 2221.2

Colouring agents

Colouring agents are used in foods and cosmetics. They are also used in medicinal preparations to improve acceptability to patients, to aid identification and prevent counterfeiting, and to increase the stability of light-sensitive drugs. Most countries restrict the nature and extent of colouring agents used for such purposes. Matters of concern that have received considerable publicity include sensitivity reactions (see Tartrazine, p. 2215.2) and hyperactive behaviour in children (see below).

The colouring agents described in this chapter can be broadly categorised into synthetic dyes and natural colours (see below). Lakes are insoluble forms of water-soluble dyes. Synthetic and natural substances elsewhere in *Martindale* that may be used as colouring agents include aluminium (p. 2439.2), (betacarotene p. 2051.1), gold (p. 2521.1), indigo carmine (p. 2532.2), lutein (p. 2079.2), lycopene (p. 2546.2), patent blue V (p. 2584.2), riboflavin (p. 2104.3), silver (p. 2615.1), and titanium dioxide (p. 1725.1).

Synthetic or artificial dyes include a wide range of organic compounds and have many industrial and domestic applications. Some are also used for colouring medicines, foods, and cosmetics.

Described in this chapter are

- Allura Red AC, p. 2168.2
- Amaranth, p. 2168.3
- Black PN, p. 2171.2
- Bordeaux B, p. 2171.3
- Brilliant Blue FCF, p. 2171.3
- Brown FK, p. 2172.1
- Brown HT, p. 2172.1
- Carbazole Violet, p. 2173.3
- Carmoisine, p. 2176.2
- CI Solvent Yellow 18, p. 2179.2
- CI Vat Orange 1, p. 2179.2
- Citrus Red 2, p. 2179.2
- Eosin, p. 2184.2
- Erythrosine, p. 2184.3
- Green S, p. 2187.3
- Orange B, p. 2200.2
- Pigment Rubine, p. 2201.3
- Ponceau 4R, p. 2204.3
- Quinoline Yellow, p. 2207.1
- Red 2G, p. 2207.2
- Sunset Yellow FCF, p. 2215.1
- Tartrazine, p. 2215.2
- Yellow 2G, p. 2221.1

Natural colours include minerals and colours from plants and animals. Compounds that are themselves natural pigments of foodstuffs, such as anthocyanins (E163; see Flavonoid Compounds, p. 2505.2) and carotenoids, may also be used. Some natural colours are also used for their flavouring or nutritional properties.

Described in this chapter are

- Annatto, p. 2169.1
- Apocarotenal, p. 2169.2
- Astaxanthin, p. 2170.1
- Beetroot Red, p. 2170.3
- Bixin, p. 2169.2
- Canthaxanthin, p. 2173.2
- Caramel, p. 2173.3
- Carmine, p. 2176.1
- Carotenoids, p. 2176.2
- Chlorophyll, p. 2178.3
- Chlorophyllin Copper Complex Sodium, p. 2178.3
- Citranaxanthin, p. 2179.2
- Cochineal, p. 2179.2
- Curcumin, p. 2180.1
- Ethyl Apocarotenoate, p. 2169.2
- Ferric Oxide, p. 2186.1
- Logwood, p. 2192.1
- Norbixin, p. 2169.2
- Raspberry, p. 2207.2
- Red Cherry, p. 2207.2
- Red-Poppy Petal, p. 2207.3
- Red-Rose Petal, p. 2207.3
- Saffron, p. 2208.2
- Turmeric, p. 2218.1
- Vegetable Carbon, p. 2219.1

Hyperactivity. The role of foods and food additives in hyperactive behaviour (p. 2314.1) has been debated for many years.

A meta-analysis[1] sought to evaluate whether artificial food colours (including carmoisine, sunset yellow, and tartrazine) contribute to the symptomatology of childhood hyperactivity in children already diagnosed with hyperactive syndromes. For the primary analysis only double-blind placebo-controlled studies were evaluated. Overall, the results supported the hypothesis that such food colours promote hyperactivity in hyperactive children as measured on behavioural ratings. However, caution was advised about making any clinical recommendations. The restrictions needed for a colour-free diet may be too much of a burden on the children and their families. Also, there is a need to find out more about the biology of artificial food colours and to ascertain whether responses depend on an allergic or pharmacological mechanism. A further study[2] in a more general population of children also found that mixtures of food additives including food colourings were associated with an increase in hyperactivity, although the European Food Safety Authority considered[3] that the results of the study were not conclusive enough to necessitate a change in the approved daily intakes for the additives involved.

1. Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr* 2004; 25: 423–34.
2. McCann D, *et al.* Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet* 2007; 370: 1560–7. Correction. *ibid.*: 1542.
3. European Food Safety Authority. Assessment of the results of the study by McCann et al. (2007) on the effect of some colours and sodium benzoate on children's behaviour: scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC). Available at: http://www.efsa.europa.eu/en/efsajournal/doc/660.pdf (accessed 17/10/11)

Diluents and vehicles

Diluents and vehicles are used to aid handling and dosing of potent active ingredients and delivery of the active ingredient to the appropriate area of the body. Many types of excipient may be used, depending upon the required function.

In *oral solid dosage forms* such as capsules and tablets, diluents are used to provide bulk and enable accurate dosing of potent ingredients. Lactose is often used, and other sugar compounds, such as dextrin, glucose, sucrose, and sorbitol, may also be used. Inorganic compounds such as silicates, calcium salts, magnesium salts, and sodium or potassium chloride are also used, although the effect of the electrolyte content needs to be considered.

Diluents used for *oral or parenteral liquid formulations* include water and aqueous solutions, alcoholic solutions, and oils and other nonaqueous liquids. The active ingredient may be dissolved or suspended in the vehicle.

Vehicles used as *cream and ointment bases* include petroleum hydrocarbons, animal fats and waxes, vegetable oils, and silicones. They may act as inert carriers, or may have emulsifying, emollient, or humectant properties. Macrogols (p. 2547.3) and other glycols may also be used.

For *suppositories*, glyceride fatty bases or macrogols are mainly used.

Vehicles used as *bulking agents for freeze-drying* include creatinine, mannitol (p. 1427.3), and polydextrose.

Described in this chapter are

- Alkyl Benzoate, p. 2168.1
- Beeswax, p. 2170.2
- Calcium Sulfate, p. 2173.1
- Candelilla Wax, p. 2173.2
- Cellulose, p. 2177.1
- Cetostearyl Alcohol, p. 2178.1
- Cetyl Alcohol, p. 2178.2
- Cetyl Esters, p. 2178.2
- Cholesterol, p. 2179.1
- Coconut Oil, p. 2179.3
- Cottonseed Oil, p. 2180.1
- Creatinine, p. 2180.1
- Dextrates, p. 2181.1
- Dimethyl Sulfoxide, p. 2182.2
- Emulsifying Wax, p. 2184.1
- Erythritol, p. 2184.3
- Ethyl Oleate, p. 2185.1
- Glyceryl Palmitostearate, p. 2187.2
- Hard Fat, p. 2188.1
- Hard Paraffin, p. 2188.1
- Isopropyl Myristate, p. 2190.3
- Isopropyl Palmitate, p. 2191.1
- Macrogol Monomethyl Ethers, p. 2194.2
- Liquid Paraffin, p. 2191.2
- Microcrystalline Wax, p. 2198.1
- Myristyl Alcohol, p. 2198.3
- Oleic Acid, p. 2200.1
- Oleyl Alcohol, p. 2200.1
- Palm Oil, p. 2200.2
- Polydextrose, p. 2202.2
- Shea Butter, p. 2208.2
- Silicones, p. 2209.2
- Soft Paraffin, p. 2211.3
- Squalane, p. 2213.3
- Stearyl Alcohol, p. 2214.2
- Theobroma, p. 2216.1
- Theobroma Oil, p. 2216.1
- Wool Alcohols, p. 2219.2
- Wool Fat, p. 2219.3
- Vegetable Fatty Oils, p. 2219.1

Disintegrants

Disintegrants are used to aid the break up of tablets and other oral dosage forms in the gastrointestinal tract, releasing the active ingredient and increasing the surface area available for dissolution. They are usually hydrophilic compounds such as starch (p. 2095.1), cellulose derivatives, and alginates, that swell or dissolve in water; crospovidone takes up water by a capillary action, causing the tablet to expand and disintegrate.

Described in this chapter are

- Alginic Acid, p. 2167.2
- Aluminium Magnesium Silicate, p. 2168.2
- Carmellose, p. 2175.1
- Cellulose, p. 2177.1
- Crospovidone, p. 2205.1

Hypromellose, p. 2189.2
Methylcellulose, p. 2197.3
Polacrilin, p. 2201.3
Sodium Starch Glycolate, p. 2211.2

Emulsifying and solubilising agents

Many therapeutically active ingredients are insoluble or immiscible in the vehicles most suitable for the required dosage form and excipients are needed to allow incorporation of the active ingredient and to improve the stability of the final product. Surface-active agents or surfactants are widely used as emulsifying, solubilising, suspending, or wetting agents in pharmaceutical products and in other industrial processes, as well as in cleaning and detergent preparations. Other suspending agents (see p. 2166.1) based on natural polymers or finely-divided particles also have emulsifying properties.

Surfactants are compounds that contain both a hydrophilic and a hydrophobic region within the same molecule, enabling them to reduce the interfacial tension between aqueous and non-aqueous phases so that mixing can occur; they also form a barrier to prevent droplets coalescing. Their exact properties depend upon the degree of hydrophilicity or hydrophobicity of the different regions, and they are often classified according to their *hydrophilic-lipophilic balance* (HLB). This is an arbitrary scale of values denoting the relative affinity of the surfactant for oil and water, and depends on the ratio of hydrophilic groups to hydrophobic groups in the molecule. Lipophilic surfactants have low HLB values (less than 10) and are generally used as antifoaming agents, water-in-oil emulsifying agents, and as wetting agents; hydrophilic surfactants have higher HLB values (greater than 10) and are generally used as oil-in-water emulsifying agents and solubilising agents.

The hydrophobic portion of most surfactants consists of a long chain hydrocarbon or fatty acid and the degree of hydrophobicity increases with the number of alkyl groups in the chain. Hydrophilic groups vary between the different types of surfactant and are usually responsible for the presence and nature of any charge on the molecule:

- *Anionic surfactants* dissociate in water into an amphiphilic anion and a cation (usually an alkali metal or ammonia). The amphiphilic portion generally contains an acid, sulfate, or sulfonate group, which bears the negative charge
- *Cationic surfactants* dissociate into an amphiphilic cation and an anion (usually a halogen). The amphiphilic portion generally contains an amine or quaternary ammonium group, which bears the positive charge
- *Ampholytic surfactants* contain both cationic and anionic groups and their properties are dependent on the pH
- *Nonionic surfactants* do not ionise in water and bear no charge. Hydrophilicity is provided by a non-dissociable group such as an alcohol, ether, or ester; polyethylene-oxide groups also provide hydrophilicity

Because of the way they are manufactured, many surfactants are mixtures of related compounds; the properties of a particular material may vary from one manufacturer to another and there may be variation in batches from an individual source.

Ampholytic (amphoteric) surfactants have the detergent properties of anionic surfactants and the disinfectant properties of cationic surfactants. Their activity depends on the pH of the media in which they are used. Compounds used include aminocarboxylic acids, aminopropionic acid derivatives, imidazoline derivatives, and dodicin. Long-chain betaines are sometimes classed as ampholytic surfactants.

When the strength of the cationic portion of the molecule is equivalent to that of the anionic portion the isoelectric point occurs at pH 7 and the molecule is said to be balanced. Balanced ampholytic surfactants are reputed to be non-irritant to the eyes and skin and have therefore been used in baby shampoos.

Anionic surfactants have both emulsifying and cleansing properties and are mainly used as detergents, although some are used as emulsifiers in pharmaceuticals and in the cosmetic and food industries. Many of the anionic surfactants used are *soaps* (salts of fatty acids) and have traditionally been produced by the alkaline hydrolysis of fatty acid esters in natural fats and oils (saponification). Anionic surfactants used in pharmaceutical preparations include:

- *Alkali-metal soaps* (monovalent alkyl carboxylates) which are the sodium and potassium salts of the higher fatty acids. They are often produced from vegetable oils (see Soft Soap, p. 2212.3) or from specific fatty acids such as stearic acid, lauric acid, or oleic acid; animal fats such as tallow may also be used. They are generally water-soluble but produce insoluble deposits with hard water; they may also irritate the skin. *Ammonium soaps* have similar properties and have also been used
- *Metallic soaps* (polyvalent alkyl carboxylates), the calcium, zinc, magnesium, and aluminium salts of the higher fatty acids. They are oil-soluble and their main pharmaceutical application is as lubricants for tablet and capsule manufacturing. They produce water-in-oil emulsions and are often formed by chemical reaction during the preparation of the emulsion
- *Amine soaps*, which are the amine salts of fatty acids and include trolamine (triethanolamine) stearate and diolamine (diethanolamine) stearate. They are mainly used in cosmetic and personal care products
- *Ester carboxylates*, which are salts of fatty acids esterified with hydroxyacids or dicarboxylic acids; they include sodium stearoyl-lactylate and sodium stearyl fumarate
- *Alkyl sulfates* (sulfated fatty alcohols; alkyl ester sulfates), such as sodium laurilsulfate (p. 2210.3), which are the salts of sulfuric acid esters of fatty alcohols. They are widely used as detergents, wetting agents, and lubricants. *Alkyl ether sulfates* (ethoxylated alkyl sulfates) are similar compounds but the fatty alcohols are ethoxylated; examples include sodium laureth sulfate
- *Sulfated oils*, which are vegetable and animal oils and fats that have been treated with sulfuric acid and then neutralised. Sulfated castor oil (neutralised with sodium hydroxide; see p. 2215.1) has been widely used.
- *Sulfonated compounds*, including alkyl sulfonates such as sodium caprylyl sulfonate and sodium cocoyl isetionate, and alkyl aryl sulfonates such as sodium dodecylbenzenesulfonate. Salts of sulfonated carboxylic acids such as sodium lauril sulfoacetate and disodium lauril sulfosuccinate are also used; docusate sodium (sodium dioctyl sulfosuccinate; p. 1836.2) has both medicinal and pharmaceutical uses
- *Alkyl phosphates*, including alkyl ester phosphates such as sodium lauryl phosphate and alkyl ether phosphates such as sodium laureth phosphate, have been used in cosmetic and personal care products
- *Alkyl sarcosides* or *sarcosinates* are fatty acid amides produced from acylation of the synthetic amino acid sarcosine (*N*-methylglycine) with fatty acids. Salts such as sodium cocoyl sarcosinate and sodium lauroyl sarcosinate have anionic surfactant properties and are used for a range of applications.

Described in this chapter are
Aluminium Monostearate, p. 2168.3
Calcium Stearoyl-lactylate, p. 2173.1
Sodium Cetostearyl Sulfate, p. 2210.2
Sodium Cocoyl Isetionate, p. 2210.3
Sodium Cocoyl Sarcosinate, p. 2210.3
Sodium Laurilsulfate, p. 2210.3
Sodium Lauroyl Isetionate, p. 2210.3
Sodium Lauroyl Sarcosinate, p. 2210.3
Sodium Oleate, p. 2211.2
Sodium Stearate, p. 2211.3
Sodium Stearoyl-lactylate, p. 2173.1
Sulfated Castor Oil, p. 2215.1

Cationic surfactants are mainly used for their disinfectant properties and are described in the chapter on Disinfectants and Preservatives (p. 1730.1), but some are used pharmaceutically for their surfactant effects.

Described in this chapter are
Tonzonium Bromide, p. 2217.1

Nonionic surfactants are widely used as pharmaceutical excipients; they also have applications in the food, cosmetic, paint, pesticide, and textile industries as well as being used as oil slick dispersants. Some nonionic surfactants are used as spermicides. Nonionic surfactants tend to be less irritant than anionic or cationic surfactants, and are generally compatible with both anionic and cationic substances; however, they reduce the antimicrobial action of many preservatives.

The range of nonionic surfactants used is large and classification is not always easy, particularly as they are often used as mixtures. Many of them are complex molecules and nomenclature may be confusing; various systems are used and there are many inconsistencies, making precise identification difficult. Most of the compounds used are esters of glycols (diols), glycerol (a triol), or other polyalcohols with fatty acids, or ethers of glycols with fatty alcohols. The main groups used are described below; examples are given in Table 1 (p. 2165). *Higher fatty acid acids and alcohols* also have nonionic surfactant properties, but are mainly used for other purposes.

- *Glycol and glycerol (glyceryl) esters*. Simple esters of fatty alcohols and fatty acids have some surfactant properties but this can be improved by further hydroxyl or ester groups. Glycol and glycerol esters (mono-esters of ethylene glycol, diethylene glycol, and propylene glycol, and mono- or di-esters of glycerol) contain both ester and hydroxyl groups and are widely used as nonionic surfactants. They have relatively few hydroxyl groups and hydrophobic properties therefore predominate. They are poor emulsifying agents if used alone, though they are useful stabilisers for both oil-in-water and water-in-oil emulsions. 'Self-emulsifying' products may be formed by addition of a small amount of soap or a similar surfactant and these are capable of producing satisfactory oil-in-water emulsions. Compounds used may be based on a single fatty acid or a mixture of fatty acids; mixed glycerol esters in which the glycerol is esterified partl / with a fatty acid and partly with acetic aci l (*acetoglycerides*) are also used.
- *Macrogol esters*. Polyethoxylation of glycols provide s additional hydrophilicity, which increases with th : degree of ethoxylation, and fatty acid esters with a wid : range of macrogols (polyethylene glycols) are usec . Increased ethoxylation produces efficient oil-in-wate : emulsifying agents, which may also be used as wettin ; and solubilising agents. Mixtures of macrogol an l glycerol esters (*macrogolglycerides*) and *polyethoxylate l glycerol esters* (esters of macrogol glycerol ethers) are als used.
- *Glycol ethers*. Ethers of glycols with fatty alcohols ar : generally included in the same class as macrogol ether ; and are used similarly. Glycol ethers with short-chai alcohols such as methyl alcohol and ethyl alcohol ar : used as solvents and solubilising agents.
- *Macrogol ethers*. Ethers of macrogols with fatty alcohol ; (*macrogol alkyl ethers*) or alkylphenols (*macrogol ar l ethers*) have similar properties to macrogol esters but th : ether linkage is more stable to hydrolysis makin ; macrogol ethers more resistant to acids and alkali : . Macrogol ethers with short-chain alcohols are also usec . particularly as solvents. Macrogol aryl ethers such a i octoxinols and nonoxinols are used as spermicides.
- *Polyalcohol esters*. Fatty acid esters of polyalcohols such a i glycerol polymers (polyglycerols), sorbitol, and sucros : also have nonionic surfactant properties. *Sorbitan este r* (esters of the cyclic mono- or di-anhydrides of sorbitc l with fatty acids) are oil-soluble, water-dispersible , nonionic surfactants and are effective water-in-o l emulsifiers. *Polysorbates* (polyethoxylated sorbitan esters) are more hydrophilic, water-soluble compounds and ar : used as oil-in-water emulsifying agents.
- *Poloxamers* are copolymers of polyoxyethylene an l polyoxypropylene. They are used as oil-in-wate r emulsifiers and as solubilising and wetting agents i n pharmaceutical preparations intended for internal use.

Described in this chapter are
Acetoglycerides, p. 2166.3
Diethylene Glycol Esters, p. 2182.1
Diethylene Glycol Ethers, p. 2182.2
Ethylene Glycol Esters, p. 2185.2
Glyceryl Behenate, p. 2186.2
Glyceryl Mono- and Di-esters, p. 2186.3
Glyceryl Monocaprylocaprate, p. 2186.3
Glyceryl Monolinoleate, p. 2186.3
Glyceryl Mono-oleate, p. 2187.1
Glyceryl Stearates, p. 2187.1
Macrogol Cetostearyl Ethers, p. 2192.2
Macrogol/glycerol Esters, p. 2192.3
Macrogol 6 Glyceryl Caprylocaprate, p. 2193.2
Macrogol 20 Glyceryl Monostearate, p. 2193.2
Macrogol 15 Hydroxystearate, p. 2193.3
Macrogol Laurates, p. 2193.3
Macrogol Lauril Ethers, p. 2193.3
Macrogol Monomethyl Ethers, p. 2194.2
Macrogol Oleates, p. 2194.2
Macrogol Oleyl Ethers, p. 2194.3
Macrogol 40 Sorbitol Heptaoleate, p. 2195.1
Macrogol Stearates, p. 2195.1
Macrogolglycerol Cocoates, p. 2195.2
Nonoxinols, p. 2199.1
Octoxinols, p. 2199.3
Oleyl Oleate, p. 2200.2
Palmitic Acid, p. 2200.3
Poloxamers, p. 2201.3
Polyoxyl Castor Oils, p. 2202.
Polyoxyl Hydrogenated Castor Oils, p. 2203.1
Polysorbates, p. 2203.1
Polyvinyl Alcohol, p. 2204.2
Propylene Glycol Caprylates, p. 2206.1
Propylene Glycol Diacetate, p. 2206.2
Propylene Glycol Laurates, p. 2206.2
Propylene Glycol Monopalmitostearate, p. 2206.2
Quillaia, p. 2207.1
Sorbitan Esters, p. 2213.1
Sucrose Esters, p. 2214.3
Triglycerol Diisostearate, p. 2218.1
Tyloxapol, p. 2218.2

Flavours and sweeteners

Flavours, flavour enhancers, and sweeteners are used i oral pharmaceutical preparations to improve the palatabilit of the preparation and mask the taste of the activ ingredient. In addition to those listed below, many natura synthetic, and semisynthetic compounds are used, of whic a great number are components of herbs, spices, and othe foodstuffs; aromatic oils are also used, as is chloroforr (p. 1898.1). Sugars have been widely used as sweetenin agents and are described in the chapter on Nutritiona Agents (p. 2042.1). Compounds with strongly aversiv tastes may be used as denaturing agents, that is, unpalatabl agents that are added to other substances to deter thei consumption.

Described in this chapter are
Acesulfame Potassium, p. 2166.2
Alitame, p. 2168.1
Aspartame, p. 2169.2
Aspartame Acesulfame, p. 2170.1
Benzaldehyde, p. 2171.1
Caramel, p. 2173.3
Cyclamates, p. 2180.2
Denatonium Benzoate, p. 2181.1
Dibutyl Sebacate, p. 2181.2
Erythritol, p. 2184.3
Ethyl Acetate, p. 2184.3
Ethyl Cinnamate, p. 2185.1
Ethyl Maltol, p. 2196.1
Ethyl Vanillin, p. 2185.2
Maltol, p. 2196.1
Monosodium Glutamate, p. 2198.2
Neohesperidin Dihydrochalcone, p. 2198.

Table 1. Examples of main groups of nonionic surfactants.

Glycol and Glycerol Esters	Glycerol Esters	Glyceryl Behenate Glyceryl Mono- and Di-esters Glyceryl Monocaprylocaprate Glyceryl Monolinoleate Glyceryl Mono-oleate Glyceryl Distearate Glyceryl Monostearate Glyceryl Palmitostearate
	Diethylene Glycol Esters	Diethylene Glycol Monolauarate Diethylene Glycol Mono-oleate Diethylene Glycol Monostearate Diethylene Glycol Palmitostearate
	Ethylene Glycol Esters	Ethylene Glycol Distearate Ethylene Glycol Monopalmitostearate
	Propylene Glycol Esters	Propylene Glycol Dicaprylocaprate Propylene Glycol Monocaprylate Propylene Glycol Diacetate Propylene Glycol Dilaurate Propylene Glycol Monolaurate Propylene Glycol Monopalmitostearate
Glycol Ethers	Diethylene Glycol Ethers	Diethylene Glycol Monoethyl Ether
Macrogol Derivatives	Ethoxylated Glycerol Esters	Macrogol 6 Glyceryl Caprylocaprate Macrogol 20 Glyceryl Monostearate Macrogolglycerol Cocoates Polyoxyl 35 Castor Oil Polyoxyl 40 Hydrogenated Castor Oil
	Macrogol Esters	Macrogol 15 Hydroxystearate Macrogol Laurates Macrogol Oleates Macrogol Stearates
	Macrogol/glycerol Esters	Behenoyl Macrogolglycerides Caprylocaproyl Macrogolglycerides Lauroyl Macrogolglycerides Linoleoyl Macrogolglycerides Oleoyl Macrogolglycerides Stearoyl Macrogolglycerides
	Macrogol Alkyl Ethers	Macrogol Lauril Ethers Macrogol Monomethyl Ethers Macrogol Oleyl Ethers
	Macrogol Aryl Ethers	Nonoxinol 9 Nonoxinol 10 Nonoxinol 11 Octoxinol 9 Octoxinol 10 Tyloxapol
Polyalcohol Esters	Polyglycerol Esters	Triglycerol Diisostearate
	Sorbitan Esters	Sorbitan Laurate Sorbitan Oleate Sorbitan Palmitate Sorbitan Sesquioleate Sorbitan Stearate Sorbitan Trioleate Sorbitan Tristearate
	Sorbitan Macrogol Esters	Macrogol 40 Sorbitol Heptaoleate Polysorbate 20 Polysorbate 40 Polysorbate 60 Polysorbate 80 Polysorbate 85
	Sucrose Esters	Sucrose Esters
Poloxamers		Poloxalene Poloxamer 188 Poloxamer 407

Neotame, p. 2199.1
Raspberry, p. 2207.2
Red Cherry, p. 2207.2
Saccharin, p. 2207.3
Saffron, p. 2208.2
Stevioside, p. 2214.2
Sucrose Octa-acetate, p. 2215.1
Thaumatin, p. 2216.1
Theobroma, p. 2216.1
Tributyl Acetylcitrate, p. 2217.2
Vanilla, p. 2218.3
Vanillin, p. 2218.3
Xylitol, p. 2220.3

Glidants and lubricants

Glidants are used to improve the flow of powders during tablet and capsule manufacturing by reducing friction and adhesion between particles; they may also be used as anticaking agents. Colloidal anhydrous silicon and other silica compounds, including calcium silicate (p. 1784.3) and magnesium silicate, are often used. Lubricants reduce friction between powders and metal surfaces and also have an important role in preventing adherence during the manufacturing process. Most lubricants are hydrophobic compounds, and long-chain fatty acids, particularly stearic acid and its salts, are most widely used; their main disadvantage is that they may slow disintegration and dissolution of the dosage form in the body. The properties of glidants and lubricants differ, although some compounds, such as starch (p. 2095.1) and talc (p. 1722.2), have both actions.

Described in this chapter are

Calcium Stearate, p. 2172.3
Glyceryl Behenate, p. 2186.2
Glyceryl Monostearate, p. 2187.2
Glyceryl Palmitostearate, p. 2187.2
Hydrogenated Vegetable Oil, p. 2219.1
Magnesium Silicate, p. 2195.3
Magnesium Stearate, p. 2195.3
Palmitic Acid, p. 2200.3
Silicon Dioxide, Colloidal, p. 2209.1
Sodium Stearyl Fumarate, p. 2211.3
Sodium Laurilsulfate, p. 2210.3
Stearic Acid, p. 2214.1
Zinc Stearate, p. 2221.2

Plasticisers

Plasticisers or softeners are relatively low-molecular-weight compounds that are used to improve the physical and mechanical properties of films by increasing the mobility of the polymer chains. They may reduce the temperature at which a polymer changes from a hard to a soft substance. Plasticisers are also used in soft gelatin capsules. Compounds used include glycerol (p. 2517.2), glycols and macrogols (p. 2547.3), and sorbitol (p. 2092.1); organic esters such as citrates, phthalates, and sebacates; and oils and glycerides. Triacetin (p. 596.2), which has antifungal properties, has also been used.

Described in this chapter are

Acetyltriethyl Citrate, p. 2167.1
Coconut Oil, p. 2179.3
Diacetylated Monoglycerides, p. 2166.3
Dibutyl Sebacate, p. 2181.2
Diethyl Phthalate, p. 2181.3
Macrogol Monomethyl Ethers, p. 2194.2
Propylene Glycol, p. 2205.2
Triethyl Citrate, p. 2218.1
Tributyl Acetylcitrate, p. 2217.2
Tributyl Citrate, p. 2217.2
Tri-*n*-butyl Phosphate, p. 2217.2

Preservatives

Preservatives are used in pharmaceutical preparations to prevent chemical or microbial degradation. They include antoxidants and antimicrobial preservatives, and are described in the chapter on Disinfectants and Preservatives, p. 1730.1.

Propellants

Propellants are used to aid delivery of the active ingredient in aerosol preparations. Some are described in the chapter on Gases, p. 1797.1.

Solvents

Solvents may be used both in the manufacturing process for solid pharmaceutical preparations and to enable active ingredients to be given in liquid form. Water (p. 2646.2) and aqueous electrolytes (p. 1775.1) are widely used, but many active ingredients are not soluble in aqueous solutions and organic solvents are therefore also used. These include alcohols, chlorinated hydrocarbons such as chloroform, fixed oils, glycols, and paraffins, some of which are described elsewhere in *Martindale*. Cosolvents are water-miscible organic solvents used to increase the solubility of poorly soluble ingredients and include alcohol, glycerin, macrogols, and propylene glycol.

Described in this chapter are

Acetone, p. 2166.3
Amyl Acetate, p. 2168.3
Amylene Hydrate, p. 2169.1
Butyl Alcohol, p. 2172.2
Butylene Glycol, p. 2172.2
Dichloromethane, p. 2181.2
Dimethyl Sulfoxide, p. 2182.2
Dimethylacetamide, p. 2183.2
Ethyl Acetate, p. 2184.3
Glycerol Formal, p. 2186.2
Glycofurol, p. 2187.3
Hexylene Glycol, p. 2188.3
Methyl Alcohol, p. 2196.2
Methyl Iso-butyl Ketone, p. 2197.1
N-Methylpyrrolidone, p. 2206.3
Octyldodecanol, p. 2199.3
Petroleum Spirit, p. 2201.2
Polyoxyl 35 Castor Oil, p. 2202.3
Propylene Carbonate, p. 2205.2
Propylene Glycol, p. 2205.2
Propylene Glycol Diacetate, p. 2206.2
Pyrrolidone, p. 2206.3
Solvent Ether, p. 2212.3
Xylene, p. 2220.2

Toxicity is a problem with organic solvents and may be associated with residual solvent in the pharmaceutical preparation, or with acute or chronic exposure during industrial and manufacturing processes, and some **industrial solvents** are described in this chapter mainly because of this. Toxicity may follow inhalation, ingestion, or absorption through the skin. Organic solvents may be irritant to the skin and mucous membranes, and often affect the CNS. They may sensitise the myocardium to catecholamines and cardiac arrhythmias may occur. Chronic exposure may lead to central and peripheral neurotoxicity, as well as to renal toxicity and hepatotoxicity. Toxicity may also occur due to deliberate abuse of solvents. For further details of general toxicity and abuse of solvents, see under Toluene, p. 2216.2.

Described in this chapter are

Acetonitrile, p. 2167.1
Aniline, p. 2169.1
Benzene, p. 2171.1
1-Bromopropane, p. 2172.1
Butyl Acetate, p. 2172.1
Carbon Disulfide, p. 2174.2
Carbon Tetrachloride, p. 2174.3
Cyclohexane, p. 2181.1
Dichloropropane, p. 2181.3
Diethyl Phthalate, p. 2181.3
Dimethylformamide, p. 2183.2
Dioxan, p. 2183.3

Epichlorohydrin, p. 2184.2
Formamide, p. 2186.1
Hexachloroethane, p. 2188.2
n-Hexane, p. 2188.2
Isobutyl Alcohol, p. 2190.3
Kerosene, p. 2191.1
2-Methoxyethanol, p. 2196.1
Methyl Butyl Ketone, p. 2197.1
Methyl Chloride, p. 2197.2
Methyl Ethyl Ketone, p. 2197.2
Pentane, p. 2201.1
Tetrachloroethane, p. 2215.3
Tetrachloroethylene, p. 2215.3
Toluene, p. 2216.2
Trichloroethane, p. 2217.3
White Spirit, p. 2219.2

Stabilisers

Physical, chemical, and microbial stability is important for pharmaceutical preparations. Preservatives (above) and chelators (p. 1537.1) are the main excipients used to prevent chemical and microbial degradation; complexing agents such as cyclodextrins may be used to improve stability and solubility, and to aid drug delivery. Buffering agents such as citric acid (p. 2480.3), tartaric acid (p. 2626.1), and ethanolamine derivates such as trolamine (p. 2634.3) may be used to control pH; this increases stability and also may improve the tolerability of parenteral preparations. Physical stability may be provided by suspending agents and viscosity enhancers (below). Colouring agents or UV absorbers (see Dermatological Drugs and Sunscreens, p. 1681.1) may be used to improve photostability, while humectants, which are compounds with water-retaining properties, are used to reduce the evaporation of water from topical preparations.

Described in this chapter are

Calcium Saccharate, p. 2172.3
Calcium Stearoyl-lactylate, p. 2173.1
Ceratonia, p. 2178.1
Cetostearoyl Alcohol, p. 2178.1
Diethylene Glycol Monopalmitostearate, p. 2182.1
Cyclodextrins, p. 2180.3
Ethylenediamine, p. 2185.3
Ethylene Glycol Monopalmitostearate, p. 2185.2
Gentisic Acid Ethanolamide, p. 2186.2
Glyceryl Monostearate, p. 2187.2
Hexylene Glycol, p. 2188.3
Maleic Acid, p. 2195.3
Monoglyceride Citrate, p. 2198.1
Potassium Metaphosphate, p. 2204.3
Propylene Glycol, p. 2205.2
Sodium Stearoyl-lactylate, p. 2173.1
Sucrose Esters, p. 2214.3
Trehalose, p. 2217.1

Suspending agents and viscosity enhancers

Compounds used as suspending agents, gelling agents, and viscosity enhancers are usually hydrophilic polymers that have the property of increasing the viscosity of water when dissolved or dispersed. The rheological properties of the dispersions can vary widely from thin liquids to thick gels.

They have wide applications both in pharmaceutical manufacturing and in the food industry. As well as being used as thickening and suspending agents many are used in emulsions as stabilisers and in some cases as emulsifying agents; some are also used in the manufacture of tablets as disintegrants, binding and granulating agents, and for film or enteric coating.

Viscosity enhancers are also used in artificial tear and artificial saliva preparations for the management of dry eye and dry mouth respectively. Those most commonly used are carbomers, cellulose ethers such as carmellose and hypromellose, polyvinyl alcohol, and povidone. Some, such as the alginates and methylcellulose, are also used in gastrointestinal disorders. Gelatin (p. 1154.1), a blood-volume expander, is also used.

Described in this chapter are

Acacia, below
Agar, p. 2167.2
Alginic Acid, p. 2167.2
Aluminium Magnesium Silicate, p. 2168.2
Aluminium Monostearate, p. 2168.3
Bentonite, p. 2170.3
Carbomers, p. 2173.3
Carmellose, p. 2175.1
Carrageenan, p. 2176.3
Cellulose, p. 2177.1
Ceratonia, p. 2178.1
Cetostearyl Alcohol, p. 2178.1
Cetyl Alcohol, p. 2178.2
Ethylcellulose, p. 2185.2
Gellan Gum, p. 2186.1
Guaraprolose, p. 2187.3
Hyetellose, p. 2188.3
Hymetellose, p. 2189.1
Hyprolose, p. 2189.1
Hypromellose, p. 2189.2
Methylcellulose, p. 2197.3
Polyethylene Oxide, p. 2202.2
Polyvinyl Acetate, p. 2204.1
Polyvinyl Alcohol, p. 2204.2
Povidone, p. 2204.3
Silicas, p. 2208.3
Stearyl Alcohol, p. 2214.2
Tragacanth, p. 2217.1
Xanthan Gum, p. 2220.1

Acacia

Acac; Acaciae Gummi; Akaasiakumi; Akaciagummi; Arabmézga; Arabská klovatina; E414; Goma arábiga; Gomme arabique; Gomme de Sénégal; Gum Acacia; Gum Arabic; Guma arabska; Gumiarabikas; Gummi Africanum; Gummi Arabicum; Gummi Arabisches; Gummi Mimosae; Акация; Гума арабика; Гуммиарабик.

CAS — 9000-01-5.

UNII — 5C5403N26O.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Acacia). The air-hardened gummy exudate from the trunk and branches of *Acacia senegal*, other species of *Acacia* of African origin, and *Acacia seyal*. Yellowish-white, yellow, or pale amber tears, sometimes with a pinkish tint. It is friable, opaque, frequently with a cracked surface, easily broken into irregular, whitish or slightly yellowish angular fragments with conchoidal fracture and a glassy and transparent appearance. Very slowly but almost completely soluble, after about 2 hours, in twice its mass of water leaving only a very small residue of vegetable particles; the liquid obtained is colourless or yellowish, dense, viscous, adhesive, translucent, and weakly acid to blue litmus paper. Practically insoluble in alcohol. Protect from light.

Ph. Eur. 8: (Acacia, Spray-dried; Acaciae Gummi Dispersione Desiccatum). It is obtained from a solution of acacia. Dissolves, rapidly and completely, after about 20 minutes, in twice its mass of water. The liquid obtained is colourless or yellowish, dense, viscous, adhesive, translucent, and weakly acid to blue litmus paper. Practically insoluble in alcohol. Protect from light.

USNF 31: (Acacia). The dried gummy exudate from the stems and branches of *Acacia senegal* (Leguminosae) or of other related African species of *Acacia*. Spheroidal tears or angular fragments of white to yellowish-white colour. It is translucent or somewhat opaque from the presence of numerous minute fissures. It is very brittle, the fractured surface is glassy and occasionally iridescent. It is also available as flakes, powder, granules, or as a spray-dried form. It is practically odourless. Insoluble in alcohol. Store in airtight containers.

Incompatibility. Incompatibilities of acacia have been reported with several substances including alcohol, aminophenazone, apomorphine, cresol, ferric salts, morphine, phenol, physostigmine, tannins, thymol, and vanillin. Acacia contains an oxidising enzyme that may affect preparations containing easily oxidised substances; the enzyme may be inactivated by heating at 100 degrees for a short time.

Uses

Acacia is used in pharmaceutical manufacturing as a suspending and emulsifying agent, as a tablet binder, and in pastilles. It is often used with tragacanth.

It is used as an emulsifier and stabiliser in the food industry.

Chronic renal failure. Oral supplementation with acacia gum has been investigated[1-4] for its potential benefit in patients with end-stage kidney disease.

1. Al-Mosawi AJ. Acacia gum supplementation of a low-protein diet in children with end-stage renal disease. *Pediatr Nephrol* 2004; 19: 1156–9.
2. Al Mosawi AJ. The use of acacia gum in end stage renal failure. *J Trop Pediatr* 2007; 53: 362–5.
3. Ali AA. *et al.* The effects of gum arabic oral treatment on the metabolic profile of chronic renal failure patients under regular haemodialysis in Central Sudan. *Nat Prod Res* 2008; 22: 12–21.
4. Al Mosawi AJ. Six-year dialysis freedom in end-stage renal disease. *Clin Exp Nephrol* 2009; 494–500.

Dental care. An acacia gel[1] has been used for the management of gingivitis and dental plaque in Ayurvedic medicine.

1. Pradeep AR. *et al.* Short-term clinical effects of commercially available gel containing *Acacia arabica*: a randomized controlled clinical trial. *Aust Dent J* 2010; 55: 65–9.

Adverse Effects

Hypersensitivity reactions have occurred rarely after inhalation or ingestion of acacia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: GR² Control Appetite Reducer; *Chile*: Vaselina Emulsionada; *Indon.*: Norflam; *Ital.*: Duofibra; Plurilac; *Singapore*: Bios Life.

Pharmacopoeial Preparations

USNF 31: Acacia Syrup.

Acesulfame Potassium *(BANM, rINNM)*

Acesulfaam-K; Acesulfam draselná sůl; Acesulfam K; Acesulfam-K; Acesulfam-Kalium; Acesulfam potasowy; Acesulfame K; Acésulfame potassique; Acesulfamkalium; Acesulfamo kalio druska; Acesulfamo potásico; Acesulfamum Kalicum; Aceszulfám-kálium; Asesulfaamikallum; E950; H73-3293; H-733293; Hoe-095K; Kalii Acesulfamum; Калия Ацесульфам.

6-Methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide potassium.

$C_4H_4KNO_4S$=201.2

CAS — 55589-62-3.

UNII — 23OV73Q5G9.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Acesulfame Potassium). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol and in acetone.

USNF 31: (Acesulfame Potassium). A white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol and in acetone. Protect from light.

Profile

Acesulfame potassium is an intense sweetener about 200 times as sweet as sucrose. It is used in beverages, cosmetics, pharmaceuticals, and foods and does not appear to be affected by cooking.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Genser Sweet†; Rondc Sweet; *Chile*: Marco Sweet Light; *UK*: Sweet 'n Low; *USA*: Mucotrol; *Venez.*: Hermesetas Gold.

Acetoglycerides

Acetylated Glycerides; E472a (acetic acid esters of mono- and diglycerides of fatty acids).

CAS — 68990-54-5 (C14-22 monoglyceride acetates).

Diacetylated Monoglycerides

Monoglicéridos diacetilados; Моноглицериды диацетилированные.

UNII — 5Z17386USF.

Pharmacopoeias. In *USNF.*

USNF 31: (Diacetylated Monoglycerides). Consists of glycerol esterified with edible fat-forming fatty acids and acetic acid. A clear liquid. Very soluble in alcohol 80%, in vegetable oils, and in mineral oils; sparingly soluble in alcohol 70%. Store in airtight containers. Protect from light.

Profile

Acetoglycerides are glycerol ester nonionic surfactants (p. 2164.2) and consist of esters of fatty acids and acetic acid with glycerol in which at least one of the hydroxyl groups is esterified with a fatty acid and at least one is esterified with acetic acid. They have been used as plasticisers, pharmaceutical excipients, and food additives.

Acetone

Aceton; Acetonă; Acetona; Acetonas; Acétone; Acetons; Acetonum; Aicéatón; Aseton; Asetoni; Atsetoon; Dimethyl Ketone; Dimetilcetona; 2-Propanona; 2-Propanone; Propanone; Ацетон.

C_3H_6O=58.08

CAS — 67-64-1.

UNII — 1364PS73AF.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Acetone). A volatile, clear, colourless liquid; the vapour is flammable. Miscible with water and with alcohol. Protect from light.

USNF 31: (Acetone). A transparent, colourless, mobile, volatile, very flammable liquid, having a characteristic odour. Sp. gr. not more than 0.789. Miscible with water, with alcohol, with chloroform, with ether, and with most volatile oils. A 50% solution in water is neutral to litmus. Store in airtight containers remote from fire.

Uses

Acetone is widely used as an industrial, pharmaceutical, and domestic solvent; it is also used as an extraction solvent in food processing.

Adverse Effects and Treatment

Inhalation of acetone vapour causes excitement followed by CNS depression with headache, restlessness, fatigue, and possibly convulsions, leading to coma and respiratory depression in severe cases. Vomiting and haematemesis may occur. There may be a latent period before the onset of symptoms of acetone poisoning. Similar symptoms may be seen after ingestion of acetone although hyperglycaemia has also been reported. Systemic toxicity may occur after extensive or prolonged skin exposure. The vapour is irritant to mucous membranes in high concentrations.

Acetone is commonly implicated in volatile substance abuse (see under Toluene, p. 2216.3).

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures. Acetone is rapidly absorbed, so gastric aspiration has little benefit unless ingestion was large and recent. Activated charcoal is also of limited value. Haemodialysis may be considered in those who do not respond to supportive therapy. Acetone has a long half-life, and observation of symptomatic patients for up to 30 hours post-ingestion has been recommended.

For the possible effect of acetone on the metabolism of acetonitrile, see under Acetonitrile, below.

Pharmacokinetics

Acetone is absorbed through the lungs and from the gastrointestinal tract, and poorly through the skin. Small amounts are oxidised to acetate and formate, but larger doses are mainly excreted unchanged in the breath, and to a much lesser extent the urine. Acetone has an elimination half-life of 17 to 27 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Sekumatic†.

Acetonitrile

Acetonitril; Acétonitrile; Acetonitrila; Acetonitrilo; Acetonitryl; Asetonitriili; Asetonitril; Cianometano; Cianuro de metilo; Cyanure de Méthyle; Etanonitrilo; Ethanenitrile; Methyl Cyanide; Metil cianuro; Ацетонитрил.

C_2H_3N=41.05

CAS — 75-05-8.

UNII — Z072S8282N.

Description. Acetonitrile is a colourless liquid with an aromatic odour. Wt per mL about 0.79 g. B.p. about 81 degrees. It emits highly toxic fumes of hydrogen cyanide when heated to decomposition or when reacted with acids or oxidising agents. Store in airtight containers.

Uses

Acetonitrile is used as an industrial solvent. It may also be present in artificial nail removers.

Adverse Effects and Treatment

As for cyanides (see Hydrocyanic Acid, p. 2156.2).

Cyanide poisoning, including a fatality, has been reported[1,2] in several infants after ingestion of artificial nail removers containing acetonitrile. As acetonitrile is slowly metabolised to cyanide, serious toxic effects may not occur until several hours after ingestion and there is the danger that these products may be confused with acetone-based nail polish removers which are less toxic. In a report[3] of an adult who died after ingestion of acetonitrile, the onset of symptoms was delayed for 24 hours. It was considered that concomitant ingestion of acetone had slowed the metabolism of acetonitrile. In another case[4] vomiting, diarrhoea, convulsions, and reduced consciousness developed in a 35-year-old man 15 hours after occupational exposure to acetonitrile. Despite treatment for cyanide poisoning, acute renal failure and rhabdomyolysis subsequently developed.

1. Caravati EM, Litovitz TL. Pediatric cyanide intoxication and death from an acetonitrile-containing cosmetic. *JAMA* 1988; 260: 3470–3.
2. Losek JD, *et al.* Cyanide poisoning from a cosmetic nail remover. *Pediatrics* 1991; 88: 337–40.
3. Boggild MD, *et al.* Acetonitrile ingestion: delayed onset of cyanide poisoning due to concurrent ingestion of acetone. *Postgrad Med J* 1990; 66: 40–1.
4. Muraki K, *et al.* Massive rhabdomyolysis and acute renal failure after acetonitrile exposure. *Intern Med* 2001; 40: 936–9.

Pharmacokinetics

Acetonitrile is absorbed by inhalation, ingestion, and through the skin. It undergoes metabolism to cyanide, which is responsible for the toxicity of acetonitrile.

Acetyltriethyl Citrate

Triethyl Acetylcitrate; Ацетилированный Триэтилцитрат.

Triethyl 2-acetoxy-1,2,3-propanetricarboxylate.

$C_{14}H_{22}O_8$=318.3

CAS — 77-89-4.

UNII — 5W8R36T90E.

Pharmacopoeias. In *USNF*.

USNF 31: (Acetyltriethyl Citrate). A clear, practically colourless, oily liquid. Insoluble in water; freely soluble in alcohol, in isopropyl alcohol, in acetone, and in toluene. Store in airtight containers.

Profile

Acetyltriethyl citrate is a citric acid ester used as a plasticiser in tablet and other pharmaceutical coatings.

Agar

Agar-agar; Agaras; Colle du Japon; E406; Gelosa; Gélose; Hán Tiān; Japanese Isinglass; Layor Carang; Arap; Arap-arap.

CAS — 9002-18-0.

UNII — 89T13OHQ2B.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Agar). Polysaccharides extracted from various species of Rhodophyceae algae, mainly those belonging to the genus *Gelidium*. It is prepared by treating the algae with boiling water; the extract is filtered while hot, concentrated, and dried. Colourless to pale yellow translucent strips, flakes, or powder; tough when damp but becoming more brittle on drying.

USNF 31: (Agar). The dried, hydrophilic, colloidal substance consisting of the polysaccharides extracted from *Gelidium cartilagineum* (Gelidiaceae), *Gracilaria confervoides* (Sphaerococcaceae), and related red algae (Class Rhodophyceae). It usually occurs in bundles consisting of thin, membranous, agglutinated strips, or in cut, flaked, or granulated forms. It may be coloured weak yellowish-orange, yellowish-grey to pale yellow, or colourless. It is tough when damp, brittle when dry. Odourless or has a slight odour. Insoluble in cold water; soluble in boiling water.

Profile

Agar is used as a suspending or thickening agent in pharmaceutical manufacturing and as an emulsifying and stabilising agent in the food industry.

It was formerly used similarly to methylcellulose (p. 2197.3) as a bulk laxative. Preparations containing agar with liquid paraffin and phenolphthalein are available to treat constipation, but the relatively small amount of agar in these probably acts solely as an emulsion stabiliser.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Agarol; *Austral.*: Colon Care; Detox Program; *Braz.*: Agarol; *Chile*: Agarol†; Vaselina Emulsionada; *Fr.*: Pseudophage; *Switz.*: Paragar; *USA*: Agoral.

Alginic Acid

Acide alginique; Ácido polimanúrico; Acidum alginicum; Algiinhapped; Algiinihappo; Alginezuur; Algínico, ácido; Algino rūgštis; Alginsäure; Alginsav; Alginsyra; Algínsýra; Alginsyre; Aljinik Asit; E400; Kwas algínowy; Kyselina algínová; Polymannuronic Acid; Альгиновая Кислота.

CAS — 9005-32-7.

ATC — A02BX13.

ATC Vet — QA02BX13.

UNII — 8C3Z4148WZ.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF*.

Ph. Eur. 8: (Alginic Acid). A mixture of polyuronic acids composed of residues of D-mannuronic and L-guluronic acids extracted from algae belonging to the Phaeophyceae. A white or pale yellowish-brown, crystalline or amorphous powder. It swells in water. Very slightly soluble or practically insoluble in alcohol; practically insoluble in organic solvents; dissolves in solutions of alkali hydroxides.

USNF 31: (Alginic Acid). A hydrophilic colloidal carbohydrate extracted with dilute alkali from various species of brown seaweeds (Phaeophyceae). A white to yellowish-white, odourless or practically odourless, fibrous powder. Insoluble in water and in organic solvents; soluble in alkaline solutions. pH of a 3% dispersion in water is between 1.5 and 3.5.

Potassium Alginate

E402; Альгинат Калия.

CAS — 9005-36-1.

ATC — A02BX13.

ATC Vet — QA02BX13.

UNII — 44ZPJ5W2J1.

Pharmacopoeias. In *USNF*.

USNF 31: (Potassium Alginate). A purified carbohydrate product extracted from various species of brown seaweeds by the use of dilute alkali. It consists chiefly of the potassium salt of alginic acid. A white to yellow, fibrous or granular powder. It dissolves in water to form a viscous, colloidal solution; insoluble in alcohol and in hydroalcoholic solutions in which the alcohol content is greater than 30% by weight; insoluble in chloroform, in ether, and in acids having a pH lower than about 3.

Propylene Glycol Alginate

E405; Propilenglicol, alginato de; Альгинат Пропиленгликоля.

Propane-1,2-diol Alginate.

ATC — A02BX13.

ATC Vet — QA02BX13.

UNII — 26CD3JZR0C.

Pharmacopoeias. In *USNF*.

USNF 31: (Propylene Glycol Alginate). A white to yellowish, practically odourless, fibrous or granular powder. Soluble in water, in solutions of dilute organic acids, and, depending on the degree of esterification, in hydroalcoholic mixtures containing up to 60% by weight of alcohol, to form stable, viscous colloidal solutions at a pH of 3.

Sodium Alginate

Algin; Alginato sódico; E401; Natrii alginas; Natrio alginatas; Natriumalginaatti; Natriumalginat; Natrium-alginát; Natrium-alginat; Sodium, alginate de; Sodium Polymannuronate; Sodyum Aljinat; Альгинат Натрия.

CAS — 9005-38-3.

ATC — A02BX13.

ATC Vet — QA02BX13.

UNII — C269C4G2ZQ.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Sodium Alginate). It consists chiefly of the sodium salt of alginic acid. A white or pale yellowish-brown powder. Slowly soluble in water, forming a viscous, colloidal solution; practically insoluble in alcohol.

USNF 31: (Sodium Alginate). A yellowish-white, practically odourless, coarse or fine powder. Soluble in water, forming a viscous, colloidal solution; insoluble in alcohol, in chloroform, and in ether, in hydroalcoholic solutions in which the alcohol content is greater than 30% by weight, and in acids when the pH of the resulting solution becomes lower than about 3. Store in airtight containers.

Incompatibility. Incompatibilities of sodium alginate have been seen with acridine derivatives, methylrosanilinium chloride, phenylmercuric acetate and nitrate, calcium salts, alcohol in concentrations greater than 5%, and heavy metals. High concentrations of electrolytes cause an increase in viscosity until salting-out of sodium alginate occurs; salting-out occurs if more than 4% of sodium chloride is present.

Profile

Alginic acid and alginates such as propylene glycol alginate and sodium alginate are used in pharmaceutical manufacturing as suspending and thickening agents. They may be used as stabilisers for oil-in-water emulsions and as binding and disintegrating agents in tablets. Various grades are usually available commercially for different applications and yield solutions of varying viscosity. A reduction in viscosity has been said to occur if sodium alginate solutions are autoclaved for sterilisation.

Alginic acid and alginates such as ammonium alginate (E403), calcium alginate (p. 1136.3), potassium alginate, propylene glycol alginate, and sodium alginate are also used as emulsifiers and stabilisers in the food industry.

Alginic acid or the alginates, magnesium alginate and sodium alginate, are given, usually formulated with an antacid, in the management of gastro-oesophageal reflux disease (p. 1807.2). Alginic acid or the alginate reacts with gastric acid to form a viscous gel (often termed a raft) that floats on top of the gastric contents. This raft then acts as a mechanical barrier to reduce reflux.

Alginates such as calcium alginate and a mixed calcium-sodium salt are used as haemostatics and wound dressings (see p. 1136.3).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alginic acid used for gastrointestinal disorders 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 02/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nu-Gel Hidrogel con Alginato†; *Canad.*: Kaltostat; Restore CalciCare; Tegaderm Alginate; *China*: Bo Lai Tong (伯来通); Wei Yi (唯易); Xin Bai Chang (欣百昌); *Irl.*: Kaltostat†; *Israel*: Nu-Gel; *Ital.*: Kaltostat; Melgisorb; Nu-Gel; *NZ*: Gaviscon; *Rus.*: Alginatol (Альгинатол); Natalsid (Натальсидум); *S.Afr.*: Gaviscon Advance†; Kaltostat; *UK*: Comfeel SeaSorb.

Multi-ingredient Preparations. *Arg.*: Comfeel SeaSorb; Hyalogran; Mylanta Reflux; Redudiet; Rennie; SeaSorb†; *Austral.*: Flaminal; Gaviscon Double Strength; Gaviscon; Gaviscon Infant Gaviscon; Mylanta Heartburn Relief; Mylanta Heartburn Relief; *Belg.*: Gastriphar; Gaviscon Advance; Gaviscon; Gaviscon; Gaviscon; Gaviscon; Rennie†; *Braz.*: Gaviscon; *Canad.*: Carboflex; Gastrifom; Gaviscon Heartburn & Acid Reflux Relief; Gaviscon Heartburn & Acid Reflux Relief; Gaviscon Maxrelief; Maalox HRF†; Stomach Comfort; *Chile*: Algicote†; Gaviscon†; Gaviscon; Reflumox; *Cz.*: Gaviscon; Gaviscon; Rennie Duo†; *Denm.*: Galieve; Gaviscon; Gaviscon; *Fin.*: Galieve; Gaviscon; Gaviscon; *Fr.*: Cicactive; Gaviscon; Gavisconell; Gavisconell; Pseudophage; Release Ag†; Topaal; Topalkan†; *Ger.*: Gaviscon Advance; Gaviscon Kautabletten; Recatol Algin; *Gr.*: Dyspagone; Gaviscon-L; Gaviscon; *Hong Kong*: Gaviscon Advance; Gaviscon Extra Strength; Gaviscon; Gaviscon; *Hung.*: Gaviscon; *India*: Acifix; Acigon; Acihit; Arfagel; Gastromax-O; Gaviscon; Raftace; Raftace; Visco; *Irl.*: Acidex; Gaviscon Advance; Gaviscon Infant; Gaviscon†; Gaviscon; Pyrogastrone†; Rennie Dual Action; Topaal; *Israel*: Algical Kalzarevet; Gaviscon Forte; Gaviscon; Kaltocarb; Kaltostat; *Ital.*: Gastrotuss; Gaviscon Advance; Gaviscon†; Gaviscon; Hyalogran; Noremifa; Silvercel; *Malaysia*: Gaviscon Advance; Gaviscon Extra Strength; Gaviscon†; Gaviscon; *Neth.*: Algicon; Algicon; Gaviscon Extra Sterk; Gaviscon Forte†; Gaviscon; Rennie Duo; *Norw.*: Galieve; Gaviscon; Gaviscon; *NZ*: Gaviscon; Gaviscon; Mylanta Heartburn Relief; *Philipp.*: Algycon; Gaviscon; *Pol.*: Gaviscon Advance; Gaviscon; Gealcid; *Port.*: Gavigard; Gaviscon; Kaltostat; *Rus.*: Gaviscon (Гевискон); Gaviscon Forte (Гевискон форте); *S.Afr.*: Gaviscon; Gaviscon; Gelacid; Gelacid; Infant Gaviscon; *Singapore*: Acticoat Absorbent; Gaviscon Advance; Gaviscon Extra Strength; Gaviscon†; Gaviscon; *Spain*: Dolcopin; Gaviscon; *Swed.*: Galieve; Gaviscon; Gaviscon; *Thai.*: Algycon; Gaviscon Dual Action; Gaviscon; Gaviscon; *Turk.*: Gaviscon Advance; Gaviscon Infant; Gaviscon; Gaviscon; Rennie Duo; *UK*: Acidex; Bisodol Extra; Bisodol Heartburn Relief; Flaminal; Gastrocote; Gaviscon Advance; Gaviscon Cool; Gaviscon Double Action; Gaviscon Infant; Gaviscon Instants; Peptac; Raft-Eze; Rennie Duo†; Setlers Heartburn & Indigestion Liquid; Topal; *Ukr.*: Gaviscon (Гавискон); Gaviscon Forte (Гавискон Форте); *USA*: Gaviscon; Genaton; Pretts Diet Aid.

Pharmacopoeial Preparations

BP 2014: Alginate Raft-forming Oral Suspension; Compound Alginate Antacid Oral Suspension.

Alitame *(USAN)*

Alitam; Alitamas; CP-54802; Алитам.

(3*S*)-Amino-*N*-[(1*R*)-1-[(2,2,4,4-tetramethyl-3-thietanyl)carbamoyl]ethyl]succinamic acid hydrate.

$C_{14}H_{25}N_3O_4S.2½H_2O$=376.5

CAS — 80863-62-3 (anhydrous alitame); 99016-42-9 (alitame hydrate).

UNII — 6KI9MS1JOG (alitame); PCE8DAE750 (anhydrous alitame).

Profile

Alitame is an intense sweetener used in foods. It is about 2000 times sweeter than sucrose.

Alkyl Benzoate

Alkyl (C12-15) Benzoate; Benzoato de alquilo; C12-15 Alkyl Benzoate; Алкил бензоат.

CAS — 68411-27-8 (C_{12}-C_{15} alkyl ester).

UNII — A9EJ3J61HQ.

Pharmacopoeias. In *USNF*.

USNF 31: (Alkyl (C12-15) Benzoate). It consists of esters of a mixture of C_{12} to C_{15} primary and branched alcohols and benzoic acid (average molecular formula $C_{20}H_{32}O_2$ = 304.5). It is a clear, practically colourless, oily liquid. Insoluble in water, in glycerol, and in propylene glycol; soluble in alcohol, in acetone, in ethyl acetate, in isopropyl alcohol, in isopropyl myristate, in isopropyl palmitate, in liquid paraffin, in vegetable oils, in volatile silicones, and in wool fat. Store in airtight containers. Protect from light.

Profile

Alkyl benzoate has emollient properties. It may be used as an oily vehicle.

Allura Red AC

Allura Rood AC; Alluranpunainen; Allurarot AC; Allurarött AC; CI Food Red 17; Colour Index No. 16035; Czerwień Allura AC; E129; FD & C Red No. 40; Rojo allura AC; Rouge Allura AC; Красный Очаровательный АС.

Disodium 6-hydroxy-5-(6-methoxy-4-sulphonato-*m*-tolylazo)naphthalene-2-sulphonate.

$C_{18}H_{14}N_2Na_2O_8S_2$=496.4

CAS — 25956-17-6.

UNII — WZB9127XOA.

Profile

Allura red AC is a synthetic azo dye used as a colouring agent in medicines, cosmetics, and foodstuffs.

Aluminium Magnesium Silicate

Aluminio-magnio silikatas; Alumiinimagnesiumsilikaatti; Aluminii magnesii silicas; Aluminium-Magnesium-Silicat; Aluminium (silicate d') et de magnésium; Aluminiummagnesiumsilikat; Alumínium-magnézium-szilikát; Aluminosilicato magnésico; Aluminum Magnesium Silicate; Křemičitan hořečnato-hlinitý; Magnesium Aluminium Silicate; Magnesium Aluminum Silicate; Saponite; Магний-алюминий Кремнекислый; Алюминиевый Силикат Магния.

CAS — 1327-43-1; 12511-31-8.

UNII — 6M3P64V0NC (aluminium magnesium silicate); SUS08ZOA9S (aluminium magnesium silicate type IA); 4J2YH8VV13 (aluminium magnesium silicate type IB); XLI9KNX1FT (aluminium magnesium silicate type IC); 7LVU907546 (magnesium aluminometasilicate type I-A); 8XX1039013 (magnesium aluminometasilicate type I-B); II0CAA4909 (aluminium magnesium silicate type II-A).

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF*. *USNF* also includes Magnesium Aluminosilicate and Magnesium Aluminometasilicate.

Ph. Eur. 8: (Aluminium Magnesium Silicate). A mixture of colloidal-size particles of montmorillonite and saponite, free from grit and nonswellable ore. Almost white powder, granules, or plates. Practically insoluble in water and in organic solvents; swells in water to form a colloidal dispersion. A 5% dispersion in water has a pH of 9.0 to 10.0.

USNF 31: (Magnesium Aluminum Silicate). A blend of colloidal montmorillonite and saponite that has been processed to remove grit and nonswellable ore components. There are several types, differing in viscosity and in ratio of aluminium content to magnesium content. It is an odourless, fine (micronised) powder, small cream to tan granules, or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol; swells when added to water or glycerol. pH of a 5% suspension in water is between 9.0 and 10.0. Store in airtight containers.

USNF 31: (Magnesium Aluminosilicate). A synthetic material that contains 20.5 to 27.7% of magnesium oxide, 27.0 to 34.3% of aluminium oxide, and 14.4 to 21.7% of silicon dioxide, calculated on the dried basis. A white powder or granules having an amorphous structure. Practically insoluble in water and in alcohol; partially soluble in acids and alkalis. A 4% suspension in water has a pH of 8.5 to 10.5. Store at a temperature not exceeding 40 degrees in airtight containers.

USNF 31: (Magnesium Aluminometasilicate). A synthetic material that contains 29.1 to 35.5% of aluminium oxide, 11.4 to 14.0% of magnesium oxide, and 29.2 to 35.6% of silicon dioxide, calculated on the dried basis. It exists in two forms, Type I-A and Type I-B. A white powder or granules having an amorphous structure. Practically insoluble in water and in alcohol; partially soluble in acids and alkalis. A 4% suspension in water has a pH of 6.5 to 8.5 (Type I-A) and 8.5 to 10.5 (Type I-B). Store at a temperature not exceeding 40 degrees in airtight containers.

Profile

Aluminium magnesium silicates are mineral clays belonging to the smectite group (see p. 1887.1). They occur naturally in various forms, depending on the mineral composition and the physical structure, and may contain varying amounts of other minerals, such as calcium, sodium, and iron. Synthetic aluminium magnesium silicates are also available.

Aluminium magnesium silicates have a variety of pharmaceutical uses, including use as suspending and thickening agents, as emulsion stabilisers, and as binders and disintegrating agents in tablets.

Other smectites with similar uses include bentonite (p. 2170.3) and Fullers earth (p. 1553.2); almasilate (p. 1815.3) and attapulgite (p. 1820.1) also have uses in gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Neusilin†.

Multi-ingredient Preparations. *India*: Aglocid; Alupectin; Digere; Gelusil MPS; Gelusil Plus; *Indon.*: Flatucid†; Stomadon†; *Jpn*: Cabe 2†; *Thai.*: Diasgest; *UAE*: Alkasid.

Aluminium Monostearate

Aluminii monostearas; Aluminium, monostéarate d'; Aluminum Monostearate; Glinu monostearynian; Monoestearato de aluminio; Monostearato de alumínio; Алюминия Моностеарат.

Dihydroxy(octadecanoato-*O*-)aluminium; Dihydroxy(stearato)aluminium.

$C_{18}H_{37}AlO_4$=344.5

CAS — 7047-84-9 (aluminium monostearate); 300-92-5 (aluminium distearate); 637-12-7 (aluminium tristearate).

UNII — P98C99461E.

Pharmacopoeias. In *Jpn* and *Pol.* Also in *USNF*.

USNF 31: (Aluminum Monostearate). A compound of aluminium with a mixture of solid organic acids obtained from fats and consisting mainly of variable proportions of aluminium monostearate and aluminium monopalmitate. A fine, white to yellowish-white, bulky powder with a fait characteristic odour. Insoluble in water, in alcohol, and n ether.

Profile

Aluminium monostearate is a metal soap anionic surfactant (p. 2164.1) used as a gelling agent in oil-based cosmetic and pharmaceutical formulations. It may also be used as a stabiliser in cosmetic emulsions. The distearate and tristearate are also used.

Amaranth

Amarant; Amarante; Amaranto; Bordeaux S; CI Acid Red 27; CI Food Red 9; Colour Index No. 16185; E123; formerly FD & C Red No. 2; Naphtol Rot S; Амарант.

It consists mainly of trisodium 3-hydroxy-4-(4-sulphonato-1-naphthylazo)naphthalene-2,7-disulphonate.

$C_{20}H_{11}N_2Na_3O_{10}S_3$=604.5

CAS — 915-67-3.

UNII — 37R8V3X49K.

NOTE. The name amaranth is also used to refer to some species of plant in the genus *Amaranthus*, some of which have been used as a source of dyes.

Uses

Amaranth is a synthetic azo dye used as a colouring agent in medicines, foodstuffs, and cosmetics.

Adverse Effects

Carcinogenicity. Although some evidence of carcinogenicity was found in early *animal* studies, subsequent work failed to confirm these findings and in the UK amaranth is considered suitable for use as a food colour.[1]

1. **MAFF.** Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4*. London: HMSO, 1987.

Amyl Acetate

Acétate de Pentyle; Acetato de amilo; Acetato di Amile; Amylasetat; Amylacetaat; Amyyliasetaatti; Essigsäurepentylester; Pentyl Acetate (*n*-amyl acetate); Pentylacetat; Амилацетат.

$C_7H_{14}O_2$=130.2

CAS — 123-92-2 (iso-amyl acetate); 53496-15-4 (sec-amyl acetate); 628-63-7 (n-amyl acetate).

UNII — 92Q24NH7AS.

Description. Amyl acetate is a mixture of isomers, principally *iso*-, *sec*-, and *n*-amyl acetate. *iso*-Amyl acetate is a clear colourless liquid with a sharp, fruity odour. Wt per mL about 0.87 g. B.p. about 140 degrees. Slightly soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Uses

Amyl acetate is used as a pharmaceutical and industrial solvent. Isoamyl acetate is used as a flavouring in foods.

Adverse Effects and Treatment

Prolonged exposure to amyl acetate may produce headache, fatigue, and depression of the CNS. Irritation of mucous membranes may also occur.

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures; activated charcoal may be given if the patient presents within 1 hour of ingestion.

Effects on the heart. A 27-year-old man developed headache, nausea, and vomiting after using a paint containing amyl acetate as the solvent in an unventilated room.[1] Some days later chest pain and dyspnoea developed; he was admitted to hospital 2 weeks after exposure with heart failure which slowly responded to treatment.

1. Weissberg PL, Green ID. Methyl-cellulose paint possibly causing heart failure. *BMJ* 1979; ii: 1113–14.

Amylene Hydrate

Aethyldimethylmethanolum; Dimethylethyl Carbinol; Hidrato de amileno; Tertiary Amyl Alcohol; *tert*-Pentyl Alcohol; Амилгидрат.

2-Methylbutan-2-ol.

$C_5H_{12}O$=88.15.

CAS — 75-85-4.

UNII — 69C393R17Z.

Pharmacopoeias. In *USNF*.

USNF 31: (Amylene Hydrate). A clear, colourless liquid having a camphoraceous odour. Sp. gr. 0.803 to 0.807. Distilling range 97 degrees to 103 degrees. Freely soluble in water; miscible with alcohol, with chloroform, with ether, and with glycerol. Its solutions are neutral to litmus. Store in airtight containers.

Uses

Amylene hydrate is used as a pharmaceutical solvent. It was formerly used as a hypnotic.

Adverse Effects

Amylene hydrate is irritant and has a depressant effect on the CNS.

Aniline

Aminobenceno; Aminobenzeen; Aminobenzene; Aniliin; Aniliini; Anilin; Anilină; Anilna; Anilíns; Bencenamina; Benzenamine; Fenilamina; Fenüülamiin; Fenylamin; Phenylamine; Анилин.

C_6H_7N=93.13

CAS — 62-53-3.

UNII — SIR7XX2F1K.

Description. Aniline is a colourless or pale yellow oily liquid with a characteristic odour, readily darkening to brown on exposure to air and light. Wt per mL about 1.02 g. B.p. about 183 degrees. Store in airtight containers. Protect from light.

Uses

Aniline is a solvent with wide industrial applications.

Adverse Effects, Treatment, and Precautions

Inhalation, ingestion, or cutaneous absorption of aniline results in methaemoglobinaemia, with cyanosis, headache, weakness, stupor, convulsions, and coma. Irritation of the skin or mucous membranes, nausea and vomiting, and cardiac arrhythmias may occur. Haemolysis has been reported and may give rise to renal damage or jaundice. Death is usually a result of cardiovascular collapse.

Treatment may involve oxygen, methylthioninium chloride (p. 1559.1), transfusions, or possibly haemodialysis. Gastric aspiration or activated charcoal may be considered in patients who present within 1 hour of ingestion.

Bladder papillomas have been reported in workers previously exposed to aniline. Commercial aniline may be contaminated with β-naphthylamine, a potential carcinogen.

Handling. Suitable precautions should be taken to avoid skin contact with aniline as it can penetrate skin and produce systemic toxicity.

Annatto

Achiote; Anatas; Annotta; Arnotta; CI Natural Orange 4; Colour Index No. 75120; E160(b); Rocou; Roucou; Аннато.

CAS — 1393-63-1.

UNII — 6POP1V1B6O.

Bixin

β-Bixin (*all-trans*-bixin); α-Bixin (*cis*-bixin); E160(b); Биксин.

Methyl (9-*cis*)-hydrogen-6,6′-diapo-ψ,ψ-carotenedioate (*cis*-bixin).

$C_{25}H_{30}O_4$=394.5

CAS — 6983-79-5 (cis-bixin); 39937-23-0 (all-trans-bixin).

UNII — 9L7T4VB66G.

Norbixin

E160(b); β-Norbixin (*all-trans*-norbixin); α-Norbixin (*cis*-norbixin); Норбиксин.

6,6′-Diapo-ψ,ψ-carotenedioic acid.

$C_{24}H_{28}O_4$=380.5

CAS — 626-76-6 (cis-norbixin); 542-40-5 (all-trans-norbixin).

UNII — E8M59E17AI.

Uses

Annatto is a colouring agent extracted from the seeds of *Bixa orellana*. It and its derivatives, the carotenoids bixin and norbixin, are used to colour foods, drugs, and cosmetics.

Bixin and norbixin exist in both *cis*- and *trans*- forms, with the *cis*- forms being the major colouring components.

Adverse Effects

Hypersensitivity. Hypersensitivity reactions to annatto have been reported rarely, including 2 cases of anaphylaxis associated with use of annatto as a food colouring.[1,2] In both cases, sensitivity was confirmed by skin testing. A literature review also found some evidence that annatto might worsen the symptoms of recurrent urticaria, although the design of several oral challenge studies with annatto was criticised.[3]

1. Nish WA, *et al.* Anaphylaxis to annatto dye: a case report. *Ann Allergy* 1991; 66: 129–31.
2. Ebo DG, *et al.* Allergy for cheese: evidence for an IgE-mediated reaction from the natural dye annatto. *Allergy* 2009; 64: 1558–60.
3. Lucas CD, *et al.* The role of natural color additives in food allergy. *Adv Food Nutr Res* 2001; 43: 195–216.

Apocarotenal

β-Apo-8′-carotenal; Apocaroténal; β-Apo-8′-karotenal; Beta Apocarotenal; Beta Apo-8′-karotenalis; Beta-apo-8′-karotenal; Béta-apo-8′-karotenal; CI Food Orange 6; Colour Index No. 40820; E160(e); 8′-Apo-β-caroten-8′-al.

all trans-2,6,11,15-Tetramethyl-17-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8,10,12,14,16-heptadecaoctenal.

$C_{30}H_{40}O$=416.6

CAS — 1107-26-2.

UNII — V22N3E2U32.

Ethyl Apocarotenoate

CI Food Orange 7; Colour Index No. 40825; E160(f); Ethyl-8′-apo-β-caroten-8′-oate.

The ethyl ester of β-apo-8′-carotenoic acid.

$C_{32}H_{44}O_2$=460.7

CAS — 1109-11-1.

Profile

Apocarotenal and ethyl apocarotenoate are carotenoids that are used as colouring agents in foods, drugs, and cosmetics.

Aspartame *(BAN, USAN, rINN)*

APM; Aspartaami; Aspartam; Aspartamas; Aspartamo; Aspartamum; Aszpartám; E951; SC-18862; Аспартам.

Methyl *N*-L-α-aspartyl-L-phenylalaninate; 3-Amino-*N*-(α-methoxycarbonylphenethyl)succinamic acid; *N*-L-α-aspartyl-L-phenylalanine, 1-methyl ester.

$C_{14}H_{18}N_2O_5$=294.3

CAS — 22839-47-0.

UNII — Z0H242BBR1.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Aspartame). A white or almost white, slightly hygroscopic, crystalline powder. Sparingly or slightly soluble in water and in alcohol; practically insoluble in dichloromethane and in *n*-hexane. Store in airtight containers.

USNF 31: (Aspartame). White, odourless, crystalline powder having a sweet taste. Sparingly soluble in water; slightly soluble in alcohol. pH of a 0.8% solution in water is about 5.

Stability. In the presence of moisture aspartame hydrolyses to form aspartylphenylalanine and a diketopiperazine derivative, with a resulting loss of sweetness.

Uses

Aspartame is an intense sweetening agent about 180 to 200 times as sweet as sucrose. It is used in foods, beverages, and pharmaceuticals. Each g provides about 17 kJ (4 kcal).

Sickle-cell disease. It has been suggested that aspartame might have beneficial effects in sickle-cell disease.[1]

1. Manion CV, *et al.* Aspartame effect in sickle cell anemia. *Clin Pharmacol Ther* 2001; 69: 346–55.

Adverse Effects and Precautions

Excessive use of aspartame should be avoided by patients with phenylketonuria since one of its metabolic products is phenylalanine. Aspartame's sweetness is lost during prolonged cooking.

Adverse effects. The safety and adverse effects of aspartame as a pharmaceutical excipient[1,2] and in general use[3] have been reviewed.

Aspartame is hydrolysed in the gastrointestinal tract to methyl alcohol, aspartic acid, and phenylalanine. However, even with extraordinary consumption, methyl alcohol toxicity stemming from aspartame use is extremely unlikely. Aspartate concentrations in blood do not rise significantly after a very large dose (50 to 100 mg/kg) and therefore toxicity related to aspartate is also not expected to occur. Despite the similarity of aspartate to glutamate, studies in glutamate-sensitive persons have shown that they are not affected by aspartame consumption. Plasma concentrations of phenylalanine are also unlikely to be markedly elevated after modest consumption of aspartame by healthy persons but persons with phenylketonuria should avoid or limit their use of aspartame.

Adverse effects have been reported[1,2] after the use of aspartame, either as spontaneously recorded complaints from consumers or as published case reports in the medical literature. Most frequently reported problems have been headache, neuropsychiatric or behavioural symptoms, seizures, gastrointestinal symptoms, and hypersensitivity or dermatological symptoms. Available data do not provide evidence for serious widespread health consequences attendant upon the use of aspartame but it would appear that certain individuals may have an unusual sensitivity to the product. A safety review[4] by the European Commission Scientific Committee on Food (ECSCF) concluded that no causal link could be established between the consumption of aspartame and the occurrence of epilepsy or seizures, or cognition, mood and behaviour; this included individuals considered sensitive to aspartame.

Studies have confirmed aspartame's lack of effect on children's behaviour or cognitive function.[5,6]

An increased incidence of brain cancer was postulated to be related to aspartame use in one report;[7] however, the FDA[8] and the ECSCF[4] maintained that the available evidence did not support an association. Multiple malignancies have been reported[9] in *rats* given doses lower than the current acceptable daily intake of 40 or 50 mg/kg. The European Food Safety Authority assessed this study and concluded,[10] on the basis of all the available evidence, that the increased incidence of cancers in the *rats* was unrelated to aspartame treatment, and that there was no need to further review the safety of aspartame, nor to revise the established acceptable daily intake for aspartame of 40 mg/kg.

1. Golightly LK, *et al.* Pharmaceutical excipients: adverse effects associated with 'inactive' ingredients in drug products (part II). *Med Toxicol* 1988; 3: 209–40.
2. American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products: update. *Pediatrics* 1997; 99: 268–78.
3. Magnuson BA, *et al.* Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. *Crit Rev Toxicol* 2007; 37: 629–727.
4. European Commission Health and Consumer Protection Directorate-General. Opinion of the Scientific Committee on Food: update on the safety of aspartame (expressed on 4 December 2002). Available at: http://ec.europa.eu/food/fs/sc/scf/out155_en.pdf (accessed 23/08/10)
5. Shaywitz BA, *et al.* Aspartame, behavior, and cognitive function in children with attention deficit disorder. *Pediatrics* 1994; 93: 70–5.
6. Wolraich ML, *et al.* Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children. *N Engl J Med* 1994; 330: 301–7.
7. Olney JW, *et al.* Increasing brain tumor rates: is there a link to aspartame? *J Neuropathol Exp Neurol* 1996; 55: 1115–23.
8. Anonymous. Aspartame: no apparent link with brain tumours. *WHO Drug Inf* 1997; 11: 18–19.
9. Soffritti M, *et al.* First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environ Health Perspect* 2006; 114: 379–85.
10. European Food Safety Authority. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to a new long-term carcinogenicity study on aspartame. *EFSA J* 2006; 356 1–44. Available

at: http://www.efsa.europa.eu/EFSA/Scientific_Opinion/afc_op_ej356_aspartame_en1,2.pdf (accessed 03/03/08)

Breast feeding. Aspartame 50 mg/kg given orally to healthy women resulted in small but significant increases in breast milk aspartate, phenylalanine, and tyrosine concentrations.[1] However, it was noted that these levels were similar to postprandial milk samples and were unlikely to impact upon total amounts of amino acids ingested by the infant. Furthermore, the dose of aspartame given in the study was considerably higher than the projected intake of about 7.5 to 8.5 mg/kg daily, assuming all sucrose intake were replaced by aspartame, and no aspartame abuse. Nonetheless, the last available guidance from the American Academy of Pediatrics[2] considered that caution was required when aspartame was ingested by mothers where either the mother or breast-fed infant had phenylketonuria.

1. Stegink LD, *et al.* Plasma, erythrocyte and human milk levels of free amino acids in lactating women administered aspartame or lactose. *J Nutr* 1979; **109**: 2173–81.
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 19/11/04)

Pharmacokinetics

Aspartame is hydrolysed in the gastrointestinal tract to its 3 primary constituents, methyl alcohol, aspartic acid, and phenylalanine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Equalsweet; Slap; *Braz.*: Dietacil†; Finn; *Canad.*: Equal; *Chile*: Naturalist; Originalsweet; Valsweet†; *India*: Aspasweet; Equal; Lo-Kal; *Ital.*: Aspartina; Futura†; Suaviter; *NZ*: Equal†; *Rus.*: Sugarfree (Шугафри); *Thal.*: Espar; *Turk.*: Aspartil; Canderel; Demi Canderel; Diyet Tat; Hermesetas Gold†; Nutra-Tat; Sanpa; *Venez.*: Dulcosil; Edul; Hermesetas Gold.

Multi-ingredient Preparations. *Arg.*: Genser Sweet†; Rondo Sweet; *Chile*: Marco Sweet Light; *India*: Glutammune; *Ital.*: Floridral; *UK*: Sweet 'n Low; *Venez.*: Hermesetas Gold.

Aspartame Acesulfame

Аспартама Ацесульфам.

L-Phenylalanine, L-α-aspartyl-2-methyl ester, compound with 6-methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide (1:1).

$C_{18}H_{23}O_9N_3S$=457.5

CAS — 106372-55-8.

UNII — IFE6C68524.

Pharmacopoeias. In *USNF.*

USNF 31: (Aspartame Acesulfame). White, odourless, crystalline powder. Slightly soluble in water and in alcohol. It contains not less than 63.0% and not more than 66.0% of aspartame, calculated on the dried basis, and not less than 34.0% and not more than 37.0% of acesulfame, calculated as the acid form on the dried basis.

Profile

Aspartame acesulfame is a compound of aspartame (see p. 2169.2) and acesulfame (see p. 2166.2), and is used similarly in foods. It is an intense sweetener about 350 times as sweet as sucrose.

Astaxanthin

Astaksantiini; Astaksantin; Astaxanthine; Astaxantina; E161(j); Ovoester; Астаксантин.

(3*S*,3′*S*)-3,3′-Dihydroxy-β,β-carotene-4,4′-dione.

$C_{40}H_{52}O_4$=596.9

CAS — 472-61-7.

UNII — 8XPW32PR7I.

Profile

Astaxanthin is a carotenoid pigment used in fish feeds to colour the flesh of salmon and similar fish. It may be obtained synthetically or from natural sources.

Astaxanthin has also been used in dietary supplements for its antoxidant effects.

Reviews.

1. Higuera-Ciapara I, *et al.* Astaxanthin: a review of its chemistry and applications. *Crit Rev Food Sci Nutr* 2006; **46**: 185–96.
2. Pashkow FJ, *et al.* Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. *Am J Cardiol* 2008; **101**: 58D–68D.
3. Fassett RG, Coombes JS. Astaxanthin: a potential therapeutic agent in cardiovascular disease. *Mar Drugs* 2011; **9**: 447–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Astacor; Asthin; Axanthin; Axtan; *Ital.*: Sincorten-A.

Multi-ingredient Preparations. *India*: Lycocare; Lycofact Plus; *Indon.*: Astadiab; Asthin B-OND; Matoflam; Matovit AX; nutrivision; *Ital.*: Caresel; Euretin; Pentaker; *Mex.*: Drusen; *Singapore*: Nutrivision†.

Beeswax

Balmumu; Bienenwachs; Bijenwas; Bišu vasks; Bivax; Bivoks; Cera d'abella; Cera d'api; Cire d'abeille; E901; Mehiläisvaha; Méhviasz; Mesilasvaha; Pčelinji vosak; Včelí vosk; Wosk pszczeli; Čebelji vosek; Пчелиный Воск.

CAS — 8012-89-3.

White Beeswax

Baltasis vaškas; Bleached Wax; Cera alba; Cera Blanca; Cêra Branca; Cera de abejas; Cire Blanche; Cire d'abeille blanche; E901; Fehér viasz; Gebleichtes Wachs; Valkovaha; Vax, vitt; Vosk bílý; White Wax; Wosk biały; Осветлённый Пчелиный Воск.

CAS — 8012-89-3.

UNII — 7G1J5DA97F.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Beeswax, White). It is bleached yellow beeswax. It occurs as white or yellowish-white pieces or plates, translucent when thin, with an odour similar to that of yellow beeswax, though fainter and never rancid, and with a fine-grained, matt and non-crystalline fracture, becoming soft and malleable when warmed in the hand. Drop point 61 degrees to 66 degrees. Practically insoluble in water; partially soluble in hot alcohol; completely soluble in fatty and essential oils.

USNF 31: (White Wax). It is bleached and purified yellow beeswax. A yellowish-white solid, somewhat translucent in thin layers. It has a faint characteristic odour and is free from rancidity. M.p. 62 degrees to 65 degrees. Insoluble in water; sparingly soluble in cold alcohol; boiling alcohol dissolves the cerotic acid and a portion of the myricin that are constituents of the wax; completely soluble in chloroform, in ether, in fixed oils, and in volatile oils; partly soluble in cold benzene and in cold carbon disulfide; completely soluble in these liquids at about 30 degrees.

Yellow Beeswax

Cêra Amarela; Cera Amarilla; Cera de abejas amarilla; Cera Flava; Cire d'abeille jaune; Cire Jaune; E901; Gelbes Wachs; Geltonasis vaškas; Keltavaha; Refined Wax; Sárga viasz; Vax, gult; Vosk žlutý; Wosk żółty; Yellow Wax; Жёлтый Пчелиный Воск.

CAS — 8012-89-3.

UNII — 2ZA36H0S2V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Beeswax, Yellow). The wax obtained by melting with hot water the walls of the honeycomb of the bee, *Apis mellifera*, and removing the foreign matter. It occurs as yellow or light brown pieces or plates with a faint and characteristic odour of honey, and with a fine-grained, matt and non-crystalline fracture, becoming soft and malleable when warmed in the hand. Drop point 61 degrees to 66 degrees. Practically insoluble in water; partially soluble in hot alcohol; completely soluble in fatty and essential oils.

USNF 31: (Yellow Wax). The purified wax from the honeycomb of the bee, *Apis mellifera* (Apidae). It is a solid, varying in colour from yellow to greyish-brown with an agreeable honey-like odour, somewhat brittle when cold, pliable when warmed in the hand, and presenting a dull, granular, noncrystalline fracture when broken. M.p. 62 degrees to 65 degrees. Insoluble in water; sparingly soluble in cold alcohol; boiling alcohol dissolves the cerotic acid and a portion of the myricin that are constituents of the wax; completely soluble in chloroform, in ether, in fixed oils, and in volatile oils; partly soluble in cold benzene and in cold carbon disulfide; completely soluble in these liquids at about 30 degrees.

Uses

Beeswax is used as a stiffening agent in ointments and creams, and enables water to be incorporated to produce water-in-oil emulsions. It is also used as a coating in the manufacture of modified-release oral preparations. White beeswax is occasionally used to adjust the melting-point of suppositories.

A sterile preparation of white beeswax, hard paraffin, and isopropyl palmitate (Sterile Surgical Bone Wax) is used to control bleeding from damaged bone during surgery. It should not be confused with Aseptic Surgical Wax (BP 1949), also known as Horsley's Wax, which contained yellow beeswax, olive oil, and phenol in a mercuric chloride solution and was used to control haemorrhage in bone or cranial surgery.

Beeswaxes are also used in foods and cosmetics.

Adverse Effects

Granuloma formation. Use of surgical bone wax has been associated with an inflammatory response in some patients. Formation of granuloma tissue at the site of application to the orbit,[1] foot,[2] hip,[3] and sternum[4] has been reported. Seven patients developed local pain and tenderness after use of bone wax in foot surgery; further surgery to remove granulomatous tissue 4 to 52 months later resolved pain in 5 patients.[2] In another patient,[5] a large, granulomatous, retroperitoneal tumour associated with a foreign-body reaction developed 19 years after the use of bone wax on the iliac crest. In an autopsy study of 18 cadavers with evidence of sternotomy, 17 of which had macroscopic evidence of bone wax use, signs of inflammation or granuloma formation were found in all but one. The authors concluded that bone wax is non-resorbable and can cause chronic inflammation up to 10 years after application.[4] However, in a prospective randomised study[6] in 400 patients undergoing coronary bypass surgery, the application of bone wax to the sternal edges appeared to be neither unsafe nor of benefit.

1. Katz SE, Rootman J. Adverse effects of bone wax in surgery of the orbit. *Ophthal Plast Reconstr Surg* 1996; **12**: 121–6.
2. Anfinsen O-G, *et al.* Complications secondary to the use of standard bone wax in seven patients. *J Foot Ankle Surg* 1993; **32**: 505–8.
3. Lavigne M, *et al.* Bone-wax granuloma after femoral neck osteoplasty. *Can J Surg* 2008; **51**: E58–E60.
4. Sudmann B, *et al.* Histologically verified bone wax (beeswax) granuloma after median sternotomy in 17 of 18 autopsy cases. *Pathology* 2006; **38**: 138–41.
5. Verborgt O, *et al.* A retroperitoneal tumor as a late complication of the use of bone wax. *Acta Orthop Belg* 2000; **66**: 389–91.
6. Przborowski J, *et al.* Is bonewax safe and does it help? *Ann Thorac Surg* 2008; **85**: 1002–6.

Hypersensitivity. For reference to hypersensitivity reactions with bee products, including beeswax, see under Apis Mellifera, p. 2445.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Aqualane; Zoodermin Crema; *Austria*: Tiroler Steinöl; *Braz.*: Balmex; *Canad.*: Pure Gardens; *Chile*: Cold Cream Avene; *Fr.*: Cerat Inalterable; Cold Cream Naturel; Jouvence; Menolistica; *Ital.*: Bavit; Vitalux; *Philipp.*: BSI Medicated Plaster; Livermin; *USA*: Boudreaux's All Natural Butt Paste; Paladin; Palomar E; *Venez.*: Nutricap.

Pharmacopoeial Preparations

BP 2014: Paraffin Ointment;

USP 36: Rose Water Ointment; White Ointment; Yellow Ointment.

Beetroot Red

Beet Red; E162 (beetroot red or betanin); Rojo de remolacha; Rouge de betterave; Свекольный Красный.

CAS — 89957-89-1 (beetroot extract); 89957-90-4 (beetroot extract); 7659-95-2 (betanin).

NOTE. The name beetroot red has been used for an extract of *Beta vulgaris* and for betanin (betanine), its main constituent.

Profile

Beetroot red is obtained from the roots of red beets, *Beta vulgaris* var. *rubra* (Chenopodiaceae). The main colouring principle consists of betacyanins of which the glycoside betanin is the main constituent. Beetroot red is used as a colouring agent for medicines, foodstuffs, and cosmetics.

Bentonite

Bentoniet; Bentoniit; Bentoniitti; Bentonit; Bentonita; Bentonitas; Bentonitum; E558; Mineral Soap; Soap Clay; Wilkinite; Бентонит.

CAS — 1302-78-9.

UNII — A3N5ZCN45C.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF*, which also includes a purified form.

Ph. Eur. 8: (Bentonite). A natural clay containing a high proportion of montmorillonite, a native hydrated aluminium silicate in which some aluminium and silicon atoms

may be replaced by other atoms such as magnesium and iron. A very fine, homogeneous, greyish-white powder with a more or less yellowish or pinkish tint. Practically insoluble in water and in aqueous solutions, but swells with a little water forming a malleable mass.

USNF 31: (Bentonite). A native, colloidal, hydrated aluminium silicate. A very fine, odourless, hygroscopic, pale buff or cream-coloured to greyish powder, free from grit. Insoluble in water, but swells to about 12 times its volume when added to water; insoluble in, and does not swell in, organic solvents. pH of a 2% suspension in water, mixed vigorously to facilitate wetting, is between 9.5 and 10.5. Store in airtight containers.

USNF 31: (Purified Bentonite). A colloidal montmorillonite that has been processed to remove grit and nonswellable ore components. An odourless, fine, micronised powder, or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol. Swells when added to water or glycerol. pH of a 5% suspension in water is between 9.0 and 10.0. Store in airtight containers.

Profile

Bentonite is a mineral clay belonging to the smectite group (see p. 1887.1). It absorbs water readily to form sols or gels, depending on its concentration, and is used in pharmaceutical manufacturing as a suspending and stabilising agent and as an adsorbent or clarifying agent. It is also used as an anticaking agent in the food industry.

Bentonite may be used as an oral adsorbent in paraquat poisoning (p. 2159.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Indon.*: Stomagel; *Malaysia*: Clearasil Pimple Treatment; *S.Afr.*: Clearasil T†; *Singapore*: Clearasil Pimple Treatment; *Switz.*: Prevalin.

Pharmacopoeial Preparations
USNF 31: Bentonite Magma.

Benzaldehyde

Aldehído benzoico; Aldehyd benzoesowy; Benisaldehyd; Bentsaldehydi; Benzaldehids; Benzaldehid; Benzaldehido; Benzaldehit; Benzaldehyd; Benzaldéhyde; Benzaldeide; Benzaldeído; Бензальдегид.

C_7H_6O=106.1

CAS — 100-52-7.

UNII — TA269SD04T.

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2014: (Benzaldehyde). A clear colourless liquid with a characteristic odour of bitter almonds. Slightly soluble in water; miscible with alcohol and with ether. Store at a temperature not exceeding 15 degrees in well-filled containers. Protect from light.

USNF 31: (Benzaldehyde). A colourless strongly refractive liquid. Slightly soluble in water; miscible with alcohol, with ether, and with fixed and volatile oils. Store in well-filled, airtight containers. Protect from light. Avoid excessive heat.

Profile

Benzaldehyde is used as a flavour as an alternative to volatile bitter almond oil. It may cause contact dermatitis.

Preparations

Pharmacopoeial Preparations
USNF 31: Compound Benzaldehyde Elixir.

Benzene

Beinsein; Benceno; Benseen; Bensen; Bentseeni; Benzè; Benzèen; Benzen; Benzenas; Benzène; Benzeno; Benzol; Benzolas; Benzols; Cyclohexatriene; Hidruro de fenilo; Phenyl Hydride; Бензол; Бензен.

C_6H_6=78.11.

CAS — 71-43-2.

UNII — J64922108F.

NOTE. Benzene may be known by names such as 'benzina', 'benzol', 'benzole', or 'benzolum'. However, 'benzol' is also used to describe a mixture of hydrocarbons and 'benzin' or 'benzine' is used as a name for a petroleum distillate (see also Petroleum Spirit, p. 2201.2).

Description. Benzene is a clear colourless flammable liquid with a characteristic aromatic odour. Wt per mL about 0.88 g. B.p. about 80 degrees. Store in airtight containers.

Uses

Benzene was formerly applied as a pediculicide. Its use as an industrial solvent is decreasing.

Adverse Effects, Treatment, and Precautions

Symptoms of acute poisoning after inhalation or ingestion of benzene include initial excitement or euphoria followed by CNS depression with headache, dizziness, blurred vision, and ataxia, which in severe cases may progress to coma (accompanied by hyperactive reflexes), convulsions, and death from respiratory failure. Other symptoms include nausea and irritation of the mucous membranes; ventricular arrhythmias may occur. Direct skin contact with liquid benzene may result in marked irritation, and dermatitis may develop on prolonged or repeated exposure.

Prolonged industrial exposure to benzene vapour has been associated with adverse effects on the gastrointestinal tract and the CNS but in particular with marked effects on the bone marrow and blood. Decreases in the numbers of red or white blood cells or of platelets may occur, producing symptoms of headache, fatigue, anorexia, pallor, and petechiae. In severe cases pancytopenia or aplastic anaemia may develop. Leukaemia, particularly acute myeloid leukaemia, has also developed, often many years after exposure to benzene has ceased. These effects have been reported in workers exposed to relatively high concentrations of the vapour (around 200 ppm or more) but reduced red blood cell counts and anaemia have also been reported at lower concentrations. Chromosome abnormalities have been seen after prolonged exposure to benzene, particularly at the higher concentrations associated with blood dyscrasias; however, the significance of these abnormalities in the development of leukaemia is unclear.

Treatment of poisoning consists of symptomatic and supportive measures. The UK National Poisons Information Service considers that gut decontamination (gastric lavage) is contra-indicated because it may increase the risk of aspiration. In chronic poisoning, repeated blood transfusions may be necessary. Adrenaline and other sympathomimetics should be avoided because of the risk of precipitating cardiac arrhythmias.

Reviews.
1. Health and Safety Executive. Benzene. *Toxicity Review 4.* London: HMSO, 1982.
2. WHO. Benzene. *Environmental Health Criteria 150.* Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/ehc/ehc/ehc150.htm (accessed 29/06/04)
3. Khan HA. Benzene's toxicity: a consolidated short review of human and animal studies. *Hum Exp Toxicol* 2007; 26: 677–85.

Malignant neoplasms. Epidemiological data support an association between benzene exposure and acute myeloid leukaemia, but the risk after low levels of exposure (1 to 10 ppm) is less clear.[1] However, a large cohort study[2] suggested that there is an increased risk of acute myeloid leukaemia and of non-Hodgkin's lymphoma with benzene exposure at levels below 10 ppm. The general association between benzene exposure and non-Hodgkin's lymphoma was also supported by a review of case-control and cohort studies.[3]

1. Austin H, *et al.* Benzene and leukemia: a review of the literature and a risk assessment. *Am J Epidemiol* 1988; 127: 419–39.
2. Hayes RB, *et al.* Benzene and the dose-related incidence of hematologic neoplasms in China. *J Natl Cancer Inst* 1997; 89: 1065–71.
3. Smith MT, *et al.* Benzene exposure and risk of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 385–91.

Pregnancy. An evaluation of the USA National Natality and Fetal Mortality Survey noted that maternal or paternal occupational exposure to agents such as benzene was associated with an increased risk of still-birth and that paternal exposure to benzene increased the risk of low-birth-weight infants.[1]

1. Savitz DA, *et al.* Effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational-age infants. *Am J Epidemiol* 1989; 129: 1201–18.

Pharmacokinetics

Benzene is absorbed after inhalation and ingestion, but is not significantly absorbed through the skin. Some is excreted unchanged from the lungs. Oxidation to phenol and related quinol compounds occurs in the liver, the metabolites being excreted in the urine as conjugates of sulfuric or glucuronic acid.

Black PN

Briliantinis Juodasis BN; Briljantsvart BN; Briljanttimusta BN; Briljantzwart BN; Brillantschwarz BN; Brilliant Black BN; Brilliant Black PN; CI Food Black 1; Colour Index No. 28440; Czerń Brylantowa PN; E151; Fekete PN; Negro Brillante; Negro Brillante BN; Negro PN; Nero Brillante BN; Noir Brillant BN; Бриллиантовый Чёрный PN; Чёрный Блестящий PN.

It consists mainly of tetrasodium 4-acetamido-5-hydroxy-6-[7-sulphonato-4-(4-sulphonatophenylazo)-1-naphthylazo]-naphthalene-1,7-disulphonate.

$C_{28}H_{17}N_5Na_4O_{14}S_4$=867.7.

CAS — 2519-30-4.

UNII — 2WPR32U0CP.

Profile

Black PN is a synthetic diazo dye used as a colouring agent in medicines, cosmetics, and foods.

Bordeaux B

Azorubrum; Bordeaux R; Bordeos B; CI Acid Red 17; Colour Index No. 16180; Кислотный Бордо.

It consists mainly of disodium 3-hydroxy-4-(1-naphthylazo)-naphthalene-2,7-disulphonate.

$C_{20}H_{12}N_2Na_2O_7S_2$=502.4.

CAS — 5858-33-3.

Profile

Bordeaux B is a synthetic azo dye formerly used as a colouring agent for medicines and foods that has been generally replaced by other colours.

Brilliant Blue

Azul brillante; Bleu brillant; Błękit brylantowy; Blu Brillante; Briliantinis mėlynasis; Briljantblått; Briljantblauw; Brillantblau; Brillantkék.

Brilliant Blue FCF

Azul brillante FCF; Bleu brillant FCF; Blue EGS; CI Acid Blue 9; CI Food Blue 2; Colour Index No. 42090; E133; FD & C Blue No. 1; Patent Blue AC; Бриллиантовый Голубой FCF; Синий Блестящий FCF.

Disodium 4′,4″-bis(*N*-ethyl-3-sulphonatobenzylamino)triphenylmethylium-2-sulphonate.

$C_{37}H_{34}N_2Na_2O_9S_3$=792.8

CAS — 3844-45-9.

UNII — H3R47K3TBD.

Brilliant Blue G

Acid Blue 90.

$C_{47}H_{48}N_3NaO_7S_2$=854.0

CAS — 6104-58-1.

Profile

The name brilliant blue has been used for various synthetic triarylmethane (triphenylmethane) dyes. Brilliant blue FCF is used as a colouring agent in medicines, cosmetics, and foodstuffs. The related compound, brilliant blue G, is used as an ophthalmological stain. Other related dyes include sulfan blue (p. 2624.1) and patent blue V (p. 2584.2).

References.
1. Enaida H, Ishibashi T. Brilliant blue in vitreoretinal surgery. *Dev Ophthalmol* 2008; 42: 115–25.
2. Gerding H, *et al.* Intravital staining of the internal limiting membrane with a novel heavy solution of brilliant blue G. *Klin Monbl Augenheilkd* 2011; 228: 298–301.

Enteral feeds. Blue colourings such as brilliant blue FCF have been added to enteral feeds to aid the detection of pulmonary aspiration but such use has been associated with toxic effects. Blue discoloration of the skin, initially attributed to cyanosis, has been reported[1] in a child who received a large quantity of brilliant blue FCF as a colouring in an enteral feed. Abnormal systemic absorption of the dye has also been reported[2] in 2 critically ill patients, both of whom subsequently died. As of September 2003 the FDA was aware of 20 cases of blue discoloration of body fluids and skin associated with the use of blue dyes, including 12 fatalities.[3] Most cases occurred in patients with a history of sepsis, suggesting that altered intestinal permeability could be a factor.

1. Zillich AJ, *et al.* Skin discoloration with blue food colouring. *Ann Pharmacother* 2000; 34: 868–70.
2. Lucarelli MR, *et al.* Toxicity of Food Drug and Cosmetic Blue No. 1 dye in critically ill patients. *Chest* 2004; 125: 793–5.
3. Anonymous. Blue discoloration and death from FD&C Blue No. 1. *WHO Drug Inf* 2003; 17: 239–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Brilliant Peel.

Multi-ingredient Preparations. *Fr.*: Viticolor.

1-Bromopropane

n-Propyl Bromide; Propyl Bromide.
C_3H_7Br=123.0
CAS — 106-94-5.
UNII — Y9746DNE68.

Uses

1-Bromopropane is used as an industrial solvent.

Adverse Effects

1-Bromopropane is irritant. Neurotoxicity has been reported after occupational exposure. Studies in *animals* have shown reproductive toxicity.

References.

1. Ichihara G. *et al.* A survey on exposure level, health status, and biomarkers in workers exposed to 1-bromopropane. *Am J Ind Med* 2004; 45: 63–75.
2. Ichihara G. *et al.* Neurologic abnormalities in workers of a 1-bromopropane factory. *Environ Health Perspect* 2004; 112: 1319–25.
3. Majersik JJ. *et al.* Severe neurotoxicity associated with exposure to the solvent 1-bromopropane (n-propyl bromide). *Clin Toxicol* 2007; 45: 270–6.
4. Raymond LW, Ford MD. Severe illness in furniture makers using a new glue: 1-bromopropane toxicity confounded by arsenic. *J Occup Environ Med* 2007; 49: 1009–19.
5. Centers for Disease Control and Prevention (CDC). Neurologic illness associated with occupational exposure to the solvent 1-bromopropane—New Jersey and Pennsylvania, 2007-2008. *MMWR* 2008; 57: 1300–2.
6. Li W. *et al.* Dose-dependent neurologic abnormalities in workers exposed to 1-bromopropane. *J Occup Environ Med* 2010; 52: 769–77.

Brown FK

Braun FK; Brun FK; Braz FK; Chocolate Brown FK; CI Food Brown 1; E154; Marrón FK; Rudasis FK; Ruskea FK; Коричневый FK.

A mixture of: sodium 2',4'-diaminoazobenzene-4-sulphonate; sodium 2',4'-diamino-5'-methylazobenzene-4-sulphonate; disodium 4,4'-(4,6-diamino-1,3-phenylenebisazo) dibenzenesulphonate; disodium 4,4'-(2,4-diamino-1,3-phenylenebisazo) dibenzenesulphonate; disodium 4,4'-(2,4-diamino-5-methyl-1,3-phenylenebisazo) dibenzenesulphonate; trisodium 4,4',4''-(2,4-diaminobenzene-1,3,5-triazo)tribenzenesulphonate.
CAS — 8062-14-4.

Profile

Brown FK, a mixture of 6 synthetic azo dyes, is used as a colouring agent for foodstuffs.

Brown HT

Braun HT; Brun chocolat HT; Brun HT; Braz HT; Chocolate Brown HT; CI Food Brown 3; Colour Index No. 20285; Csokoládébarna HT; E155; Marrón HT; Marrone HT; Rudasis HT; Ruskea HT; Коричневый HT.

Disodium 4,4'-(2,4-dihydroxy-5-hydroxymethyl-1,3-phenylenebisazo)di(naphthalene-1-sulphonate).
$C_{27}H_{18}N_4Na_2O_9S_2$=652.6
CAS — 4553-89-3.

Profile

Brown HT, a synthetic diazo dye, is used as a colouring agent for medicines and foodstuffs.

2-Butoxyethanol

Butyl Glycol; Butyl Oxitol; EGBE; Ethyleenglycol(mono)butylether; Ethylene Glycol Butyl Ether; Ethylene Glycol Monobutyl Ether; Ethyleneglycolmonobutylether.

2-Butoxy-1-ethanol.
$C_6H_{14}O_2$=118.2
CAS — 111-76-2
UNII — 10P9XEZ9WV.

NOTE. The name Butyl Cellosolve has been used as a trade mark for 2-butoxyethanol.

Profile

2-Butoxyethanol is a glycol ether solvent with similar properties to 2-methoxyethanol (p. 2196.1).

Butyl Acetate

Acétate de Butyle; Acetato de butilo; Acetato di *n*-butile; AcOnBu; Butil-acetát; Butylacetaat; Butylacetat; Butylethanoat; Butylu octan; *N*-butyyliasetaatti; Essigsäure-*n*-butylester; Éster butílico; Etanoato de butila; Etanoato de butilo; Бутилацетат.

n-Butyl acetate.
$C_6H_{12}O_2$=116.2
CAS — 123-86-4.
UNII — 464P5N1905.

Description. Butyl acetate is a clear, colourless flammable liquid with a strong fruity odour. Wt per mL about 0.88 g. B. p. 123 degrees to 126 degrees. Slightly soluble in water; miscible with alcohol. Store in airtight containers.

Uses

Butyl acetate is used as an industrial solvent and as an extraction solvent in food processing.

Adverse Effects

Butyl acetate is irritant. High concentrations may cause CNS depression.

Butyl Alcohol

Alcohol butílico; 1-Butanol; *n*-Butanol; Butanole; Butanoli; Butanolo; 1-Butyl alcohol; *n*-Butyl Alcohol; Бутиловый Спирт.

Butan-1-ol.
$C_4H_{10}O$=74.12
CAS — 71-36-3.
UNII — 8PJ61P6TS3.

Pharmacopoeias. In *USNF*.

USNF 31: (Butyl Alcohol). A clear, colourless, mobile liquid having a characteristic, penetrating vinous odour. Soluble in water; miscible with alcohol, with ether, and with many other organic solvents. Store in airtight containers at a temperature not exceeding 40 degrees.

Uses

Butyl alcohol is used as an industrial and pharmaceutical solvent and as an extraction solvent in food processing.

Adverse Effects and Precautions

Butyl alcohol may be irritant and may cause mild CNS depression with headache, dizziness, and drowsiness.

References to the toxicity of butyl alcohol.

1. WHO. Butanols—four isomers: 1-butanol, 2-butanol, tert-butanol, isobutanol. *Environmental Health Criteria 65.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc65.htm (accessed 29/06/04)
2. WHO. 1-Butanol health and safety guide. *IPCS Health and Safety Guide 3.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg003.htm (accessed 29/06/04)
3. Bunc M. *et al.* Butanol ingestion in an airport hangar. *Hum Exp Toxicol* 2006; 25: 195–7.
4. McLain VC. Final report of the addendum to the safety assessment of *n*-butyl alcohol as used in cosmetics. *Int J Toxicol* 2008; 27 (suppl 2): 53–69.

Handling. Suitable precautions should be taken to avoid skin contact with butyl alcohol as it can penetrate skin and produce systemic toxicity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Ableed.

Butylamine

Butilamina; Butylamina; *n*-Butylamine; Butyloamina; Бутиламин.

$C_4H_{11}N$=73.14
CAS — 109-73-9.
UNII — N2QV60B4WR.

Description. Butylamine is a colourless to pale yellow flammable liquid with an ammoniacal odour. Wt per mL about 0.744 g. B.p. about 78 degrees. Miscible with water, with alcohol, and with ether. Store in airtight containers.

Uses

Butylamine is used as a solvent.

Adverse Effects and Precautions

Butylamine is irritant. Symptoms of CNS depression may occur after exposure to high concentrations of the vapour.

Handling. Suitable precautions should be taken to avoid skin contact with butylamine as it can penetrate skin and produce systemic toxicity.

Butylene Glycol

1,3-Butanediol; Butanediol; 1,3-Butylene Glycol; β-Butylene Glycol; 1,3-Dihydroxybutane; Methyltrimethylene Glycol.

Butane-1,3-diol.
$C_4H_{10}O_2$=90.12
CAS — 107-88-0.
UNII — 3XUS85K0RA.

NOTE. Do not confuse with butyl glycol, which is ethylene glycol monobutyl ether.

Profile

Butylene glycol has similar properties to propylene glycol (p. 2205.2) and is used as a solvent in pharmaceutical manufacturing. It is also used in foods and cosmetics, including preparations for hand disinfection, as a solvent and humectant and for its antimicrobial preservative properties. Hypersensitivity reactions have been reported.

The related isomer, 1,4-butylene glycol (1,4-butanediol) is used as an industrial solvent and chemical intermediate but has also been the subject of abuse (see Abuse under Adverse Effects of Sodium Oxybate, p. 1914.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Manorapid Synergy; *Ger.*: GeloBacin; Poly-Alkohol†; *Israel*: Monorapid†; Skin Des†; *Singapore*: Bio-Taches Masque†; Bio-Taches†.

Calcium Saccharate *(rINN)*

Calcii Saccharas; Calcium D-Saccharate; Sacarato cálcico; Sacarato de calcio; Saccharate de Calcium; Sucrate de Calcium; Кальция Сахарат.

Calcium D-glucarate tetrahydrate.
$C_6H_8CaO_8.4H_2O$=320.3
CAS — 5793-88-4 (anhydrous calcium saccharate); 5793-89-5 (calcium saccharate tetrahydrate).
UNII — 5ST07NLK7J (anhydrous calcium saccharate) 6AP9J91K4V (calcium saccharate tetrahydrate).

NOTE. Do not confuse with Saccharin Calcium (p. 2208.1). The names calcium saccharate and calcium sucrate have also been used to describe saccharated lime.

Pharmacopoeias. In *US*.

USP 36: (Calcium Saccharate). A white, odourless crystalline powder. Very slightly soluble in cold water and in alcohol; slightly soluble in boiling water; practically insoluble in chloroform and in ether; soluble in dilute mineral acids and in solutions of calcium gluconate.

Profile

Calcium saccharate is used as a stabilising agent in solutions of calcium gluconate for injection. Each g of calcium saccharate contains about 3.1 mmol of calcium. Calcium saccharate 8 g is equivalent to about 1 g of calcium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Calcium Fresenius; *Cz.*: Calcium Biotika; *Spain*: Suplecal.

Multi-ingredient Preparations. *Ger.*: Calcium Braun†; *Mex.*: Prevefem Complex.

Calcium Stearate

Calcii stearas; Calcium, stéarate de; Calciumstearat; E470a (sodium, potassium and calcium salts of fatty acids); Estearato de calcio; Kalcio stearatas; Kalciumstearat; Kalciumsztearát; Kalsiumstearaatti; Stearan vápenatý; Stearato di calcio; Кальция Стеарат.

Calcium octadecanoate.
CAS — 542-42-7 (calcium palmitate); 1592-23-0 (calcium stearate).
UNII — 776XM7047L.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Calcium Stearate). A mixture of calcium salts of different fatty acids consisting mainly of stearic acid ($C_{36}H_{70}CaO_4$ = 607.0) and palmitic acid ($C_{32}H_{62}CaO_4$ = 550.9) with minor proportions of other fatty acids. The fatty acid fraction contains not less than 40.0% of stearic acid and the sum of stearic acid and palmitic acids is not less than 90.0%. A fine, white or almost white, crystalline powder. Practically insoluble in water and in alcohol.

USNF 31: (Calcium Stearate). A compound of calcium with a mixture of solid organic acids obtained from fats, consisting mainly of variable proportions of calcium stearate ($C_{36}H_{70}CaO_4$ = 607.0) and calcium palmitate ($C_{32}H_{62}CaO_4$ = 550.9). A fine, white to yellowish-white bulky, unctuous powder, free from grittiness with a slight

characteristic odour. Insoluble in water, in alcohol, and in ether.

Uses

Calcium stearate is a metal soap anionic surfactant (p. 2164.1). It is used as a lubricant and anticaking agent in the manufacture of tablets and capsules and is also used in foods, cosmetics, and other industrial applications.

Adverse Effects

Acute eosinophilic pneumonia in 1 patient has been attributed to the presence of calcium stearate used as an additive in an antihistamine tablet formulation.[1]

1. Kurai J, *et al.* Acute eosinophilic pneumonia caused by calcium stearate, an additive agent for an oral antihistaminic medication. *Intern Med* 2006; **45**: 1011–16.

Calcium Stearoyl-lactylate

Calcium Stearoyl-2-lactylate; Calcium Stearyl Lactylate; Calcium Verate; E482; Стеароиллактилат Кальция.
Calcium 2-(1-Carboxyethoxy)-1-methyl-2-oxoethyloctadecanoate.
CAS — 5793-94-2.

Sodium Stearoyl-lactylate

E481; Natriumstearoyl-2-lactylaat; Natriumstearoyl-2-lactylat; Natriumstearoyyll-2-laktylaatti; Nátrium-sztearoil-2-laktilát; Sodium Stearoyl Lactate; Sodium Stearoyl-2-lactylate; Sodium Stearyl Lactylate; Стеароиллактилат Натрия.
Sodium 2-(1-Carboxyethoxy)-1-methyl-2-oxoethyloctadecanoate sodium salt.
CAS — 25383-99-7.
UNII — IN99IT31LN.

Profile

Calcium and sodium stearoyl lactylate are ester carboxylate anionic surfactants (p. 2164.1) consisting mainly of salts of stearic acid esterified with lactic acid lactate. They are used as emulsifiers and stabilisers in the food industry, including in foods for special diets; they also have pharmaceutical and cosmetic applications.

Calcium Sulfate

Calcii sulfas; Calcium, sulfate de; Calcium Sulphate; Calciumsulfat; E516; Gypsum (calcium sulfate dihydrate); Kalcija sulfāts; Kalcio sulfatas; Kalciumsulfat; Kalcium-szulfát; Kalsiumsulfaatti; Kalsiumsulfat; Kalsiyum Sülfat; Shí Gāo (calcium sulfate dihydrate); Síran vápenatý; Solfato di calcio; Sulfat de calci; Sulfato cálcico; Sulfato de Cálcio; Wapnia siarczan; Сульфат Кальция; Сернокислый Кальций.
$CaSO_4$=136.1
CAS — 7778-18-9 (anhydrous calcium sulfate); 10101-41-4 (calcium sulfate dihydrate).
UNII — WAT0DDB505 (calcium sulfate); E934B3V59H (anhydrous calcium sulfate); 4846Q921YM (calcium sulfate dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn* which specify the dihydrate. Also in *USNF* which specifies the dihydrate or the anhydrous material.

Ph. Eur. 8: (Calcium Sulfate Dihydrate). A white or almost white fine powder. Very slightly soluble in water; practically insoluble in alcohol.

USNF 31: (Calcium Sulfate). It is anhydrous or contains two molecules of water of hydration. A white to slightly yellow-white odourless fine powder. Soluble 1 in 375 of water and 1 in 485 of boiling water; soluble in 3N hydrochloric acid.

Profile

Calcium sulfate dihydrate is used as an excipient for the preparation of tablets or capsules.

Homoeopathy

Calcium sulfate has been used in homoeopathic medicines under the following names: Calcium sulfuricum; Calcarea sulphurica; Cal. sul.; Calc sulph.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Celloids CS 36†.

Multi-ingredient Preparations. *Jpn*: Eppikajutsuto; Makyokanseki to; Mokuboito; Shin'iseihaito; Shofusan; Shosaikotokakikyosekko; *Pol.*: Padma 28; *Switz.*: Arteria-vita; Padma 28; Padmed Circosan; *UK*: Padma 28; Padma Circosan; *Ukr.*: Pregnalac (Прегналак)†.

Homoeopathic Preparations. *Austria*: Asinis; *Canad.*: Combinaison†; Diamite; Hylands Bioplasma; Melange†; Nuage Bioplasma†; *Ger.*: Drufusan N†; Drufusan; Sinuselect N; *Russ.*: Asinis (Асинис); *Ukr.*: Asinis (Асинис).

Candelilla Wax

Candelillawachs; Cire de Candelilla; E902; Kandelilla viasz; Канделильский Воск.
CAS — 8006-44-8.
UNII — WL0328HX19.

Pharmacopoeias. In *USNF*.

USNF 31: (Candelilla Wax). The purified wax from the leaves of the plant *Euphorbia antisyphilitica*. It is a hard, yellowish-brown, opaque to translucent wax. M.p. between 68.5 degrees and 72.5 degrees. Insoluble in water; soluble in chloroform and in toluene.

Profile

Candelilla wax is used as a pharmaceutical excipient and in the food industry.

Canthaxanthin

Cantaxantina; Canthaxanthine; Canthaxantinum; CI Food Orange 8; Colour Index No. 40850; E161(g); Kantaksantiini; Kantaksantin; Kantaksantinas; Kantaxantin; Кантаксантин.
β,β-Carotene-4,4′-dione.
$C_{40}H_{52}O_2$=564.9
CAS — 514-78-3.
UNII — 4C3C6403MU.

Uses

Canthaxanthin is a carotenoid but unlike betacarotene or apocarotenal it has no vitamin A activity. It has selected uses as a food colouring and may be given to salmon, trout, and poultry to colour their flesh, and to laying hens to colour the yolks of their eggs. It is also used to colour medicines and cosmetics.

Canthaxanthin has also been given orally to produce an artificial suntan, and as an adjunct to betacarotene in the management of erythropoietic protoporphyria (see Porphyrias under Haem Derivatives, p. 1556.1).

Adverse Effects

Use of canthaxanthin as a food colouring is generally regarded as safe, although there have been concerns about hepatotoxicity and urticaria has been reported. Oral doses of canthaxanthin have been associated with retinal toxicity. For further details, see below.

Canthaxanthin has been associated with retinal changes involving accumulation of bright yellow particles around the macula ('gold speck' maculopathy), and alterations in eye function and visual deterioration have occurred.[1-3] Although these reports have related to oral use either for the production of an artificial tan by means of pigment deposition in the skin or for the medical treatment of erythropoietic protoporphyria, there has been concern about the use of canthaxanthin as a food colouring, and it was suggested that it should be restricted to use as a feed additive for farmed salmon and trout in order to produce a coloration of the fish flesh.[1] The results of long-term toxicity studies in *animals* also led to concern[2] about the potential for hepatotoxicity. However, subsequent studies failed to confirm hepatotoxicity in humans and it is now allowed as a food colouring,[4] although its uses are restricted in some countries. Canthaxanthin is one of several food colourings that have been reported to provoke chronic urticaria.[5]

There has also been a report of fatal aplastic anaemia in a patient who took canthaxanthin in order to produce an artificial tan.[6]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4*. London: HMSO, 1987.
2. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 789* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_789.pdf (accessed 25/05/07)
3. Hueber A, *et al.* Canthaxanthin retinopathy: long-term observations. *Ophthalmic Res* 2011; **46**: 103–106.
4. FAO/WHO. Evaluation of certain food additives and contaminants: forty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 859* 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_859.pdf (accessed 25/05/07)
5. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; **104**: 369–81.
6. Bluhm R, *et al.* Aplastic anemia associated with canthaxanthin ingested for 'tanning' purposes. *JAMA* 1990; **264**: 1141–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bronsual; Bronzearte.

Multi-ingredient Preparations. *Arg.*: Sol Bronce Vital.

Capryloyl Glycine

Caprilloyl Glycine; Caprylylglycine.
N-(1-Oxo-octyl)glycine.
$C_{10}H_{19}NO_3$=201.3
CAS — 14246-53-8.
UNII — 8TYSYO42NJ.

Profile

Capryloyl glycine is an amino acid fatty acid ester (lipoamino acid) derived from the amino acid glycine and caprylic acid. It is used as a moisturiser in cosmetic products and may also have antibacterial properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Saliker; *Chile*: Kerium Anticaspa -Caspa Grasa; Kerium Anticaspa -Caspa Seca; Kerium Anticaspa Intensivo.

Caramel

Burnt Sugar; Caramelo; Karamell; Sacch. Ust.; Saccharum Ustum; Sockerkulör; Sokerikulööri; Sukkerkulør; Zuckercouleur; Жжёный Сахар; Сахарный Колер.
CAS — 8028-89-5.
UNII — T9D99G2B1R.

Pharmacopoeias. In *USNF*.

USNF 31: (Caramel). A concentrated solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a uniform dark brown mass results, a small amount of alkali or of alkaline carbonate or a trace of mineral acid being added while heating. It is a thick, dark brown liquid, having the characteristic odour of burnt sugar, and a pleasant bitter taste. One part dissolved in 1000 parts of water yields a clear solution having a distinct yellowish-orange colour. The colour of this solution is not changed and no precipitate is formed after exposure to sunlight for 6 hours. When spread as a thin layer on a glass plate, it appears homogeneous, reddish-brown, and transparent. Miscible with water; immiscible with ether, with chloroform, with acetone, with petroleum spirit, and with benzene; soluble in dilute alcohol up to 55%. Store in airtight containers.

Profile

Caramels are used in foods, medicines, and cosmetics to produce pale yellow to dark brown colours. They have no calorific value. They are complex mixtures of compounds prepared by heating carbohydrates (food-grade sweeteners consisting of glucose, fructose, or polymers of these) either alone or in the presence of acids or alkalis (food-grade citric or sulfuric acids or calcium, potassium, or sodium hydroxides, or mixtures of these). The caramels can be classified according to the reactants used in the manufacturing process:

Class I (E150a, plain caramel, spirit caramel, or caustic caramel); no ammonium or sulfite compounds are used.

Class II (E150b or caustic sulfite caramel); sulfite compounds used but not ammonium compounds.

Class III (E150c, ammonia caramel, or beer caramel); ammonium compounds used but not sulfite compounds

Class IV (E150d, sulfite ammonia caramel, or soft-drink caramel); both ammonium and sulfite compounds used.

Some caramels also have flavouring properties.

Carbazole Violet

Colour Index No. 51319; Permanent Violet RL; Pigment Violet 23; Фиолетовый Карбазол.
8,18-Dichloro-5,15-diethyl-5,15-dihydrodiindolo(3,2-*b*:3′,2′-*m*)triphenodioxazine.
$C_{34}H_{22}Cl_2N_4O_2$=589.5
CAS — 6358-30-1.
UNII — 8U8Z6628KF.

Profile

Carbazole violet is a synthetic dye used as a colouring agent in cosmetics and contact lenses.

Carbomers

Acrylic Acid Polymers; Carbomera; Carbomere; Carbomères; Carbómeros; Carbopols; Carboxipolimetilenos; Carboxypolymethylene; Carboxyvinyl Polymers; Carpolenos; Karbo-

meerit; Karbomerai; Karbomerek; Karbomeren; Karbomerler; Karbomery; Poliakrilic Asit; Polimeros de carboxivinilo; Polyacrylic Acid; Карбомеры.
CAS — 9003-01-4; 54182-57-9.
UNII — 4Q93RCW27E (carbomer 940).

NOTE. Carbomer is *BAN, USAN,* and *rINN.*

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *Int. USNF* has separate monographs for a range of carbomers.

USNF also includes Carbomer Copolymer and Carbomer Interpolymer.

Ph. Eur. 8: (Carbomers). High-molecular-weight polymers of acrylic acid cross-linked with polyalkenyl ethers of sugars or polyalcohols. They are produced in several grades characterised by the viscosity of a defined solution. White or almost white, fluffy, hygroscopic powders. They swell in water and in other polar solvents after dispersion and neutralisation with sodium hydroxide solution. Store in airtight containers.

USNF 31: (Carbomer 934; Carbomer 934P; Carbomer 940; Carbomer 941; Carbomer 1342). Carbomers are high-molecular-weight polymers of acrylic acid cross-linked with allyl ethers of pentaerythritol. The viscosity of a neutralised aqueous dispersion for each carbomer is:

- Carbomer 934 (0.5%), 30 500 to 39 400 cP
- Carbomer 934P (0.5%), 29 400 to 39 400 cP
- Carbomer 940 (0.5%), 40 000 to 60 000 cP
- Carbomer 941 (0.5%), 4000 to 11 000 cP
- Carbomer 1342 (1.0%), 9500 to 26 500 cP

They are white, fluffy, hygroscopic powders having a slight characteristic odour. pH of a 1% dispersion in water is about 3. When neutralised with alkali hydroxides or with amines, they dissolve in water, in alcohol, and in glycerol. Store in airtight containers.

USNF 31: (Carbomer Copolymer). A high-molecular-weight copolymer of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of polyalcohols. Different types of Carbomer Copolymer are characterised by the viscosity of a defined solution. Carbomer Copolymer does not constitute the official title when benzene is used in the manufacturing process, in which case the name will be Carbomer 1342 if it complies with the requirements of that monograph. Store in airtight containers at a temperature not exceeding 45 degrees.

USNF 31: (Carbomer Interpolymer). A carbomer homopolymer or copolymer that contains a block copolymer of macrogol and a long chain alkyl acid ester. Different types of Carbomer Interpolymer are characterised by the viscosity of a defined solution. Store in airtight containers at a temperature not exceeding 45 degrees.

Profile

Carbomers are used in pharmaceutical manufacturing as suspending agents, gel bases, emulsifiers, and binding agents in tablets.

Carbomers, in liquid gel formulations containing typically 0.2 or 0.3%, are used topically as tear substitutes in the management of dry eye (p. 2190.1).

Carbomers have also been investigated as vaginal spermicides and microbicides.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acrylarm; Allvialux; Gimonte XXI; Liposic Phoenix Lagrimas; Refresh Gel; Siccafluid; Viscotears; *Austral.*: Poly Gel; Viscotears; *Austria*: Aqua-Tears; Vidisic; *Belg.*: Alcon Eye Gel; Lacrinorm; Liposic; Ocugel; Thilo Tears; Vidisic; *Braz.*: Refresh Gel; Vidisic; Viscotears; *Canad.*: Tear-Gel†; *Chile*: Feels; Lacryvisc; Nicotears; Viscotears; *China*: Liposic (立宝舒); Vidisic (唯地息); *Cz.*: Oftagel; Vidisic; *Denm.*: Oftagel; Viscotears; *Fin.*: Oftagel; Viscotears; *Fr.*: Aquarest; Civigel; Gel-Larmes; Lacrinorm; Lacryvisc; Liposic; Siccafluid; *Ger.*: Arufil C†; Lacrigel C†; Liposic; Liquigel; MuGard; Siccapos; Thilo-Tears; Vidisic; Visc-Ophtal; Visco-Vision; *Gr.*: Dacrio Gel; Liposic; Siccafluid; Tear drops; Thilogel; Viscoter; *Hong Kong*: Lacryvisc; Liposic; Viscotears†; *Hung.*: Oftagel; Vidisic; *Irl.*: GelTears; Liposic; Liquivisc; Vidisic; *Israel*: Liposic; Viscotears; *Ital.*: Dacriogel; Dropgel; Lacrigel; Lacrinorm; Lipovisc; Siccafluid; Viscotirs; *Malaysia*: Siccapos; *Mex.*: Acrylarm; Conforgel; Lacryvisc; Lipolac; Refresh; Viscotears; *Mon.*: Lacrifluid; Lacrigel; *Neth.*: Dry Eye Gel; Lacrinorm; Liposic; Siccafluid; Siccafree; Siccamed; Thilo-Tears; Vidisic; *Norw.*: Oftagel; Viscotears; *NZ*: Viscotears; *Philipp.*: Lacryvisc; Lipolin; Siccafluid; Vidisic; *Pol.*: Oftagel; Oftipan; Vidisic; *Port.*: Lacryvisc; Liposic; Siccafluid; Vidisic; *Rus.*: Oftagel (Офтагель); Vidisic (Видисик); *S.Afr.*: Teargel; *Singapore*: Lacryvisc; Vidisic; *Spain*: Lacryvisc; Lipolac; Ofarsin; Siccafluid; Viscotears; *Swed.*: Oftagel; Viscotears; *Switz.*: Fluidose; Lacrifluid; Lacrinorm; Lacryvisc; Liposic; Siccafluid; Viscotears; *Thai.*: Lacryvisc; Liposic; Vidisic; *Turk.*: Lacryvisc; Lipotears; Siccafluid; Siccapos; Thilo-Tears; Viscotears; *UK*: Artelac Nighttime; Clinitas Gel; GelTears; Liposic†; Liquivisc; Lumecare Long Lasting; Viscotears; *Ukr.*: Vidisic (Видисик); *Venez.*: Acrylarm; Lacryvisc; Siccafluid; Viscotears.

Multi-ingredient Preparations. *Arg.*: Caien†; Latlas Fresh; Latlas; *Austral.*: Genteal; Visine Professional†; *Braz.*: Liposic; *Chile*: Gelsolets; *Cz.*: Hypotears; *Fin.*: Lakrimont; *Ger.*: Repithel; Visine Trockene Augen; Visine zur Nacht; *Hong Kong*: Clinac OC; *Indon.*: Genteal; Oculotect; Sodermix; *Ital.*: Dropyal; Recugel; Visine Dry Eyes†; *Malaysia*: Genteal; *Pol.*: Oculotect; *Port.*: Hidratante VG; *Switz.*: Lacrycon; *Thai.*: Genteal; *USA*: Maxilube; Mimyx†; *Venez.*: Genteal.

Pharmacopoeial Preparations
BP 2014: Carbomer Eye Drops.

Carbon Disulfide

Bisulfuro de carbono; Carbon Bisulphide; Carbon Disulphide; Carboneï Sulfidum; Carboneum Bisulfuratum; Carboneum Sulfuratum; Dissulfeto de carbono; Disulfuro de carbono; Dwusiarczek węgla; Hiilidisulfidi; Karbondisulfid; Karbondisülfür; Kohlenstoffdisulfid; Koldisulfid; Koolstofdisulfide; Ogljikov Disulfid; Schwefelkohlenstoff; Sêrogleklis; Sirouhlík; Solfuro di carbonio; Sulfură de carbon; Sulfure de carbone; Szén-diszulfid; Węgla disiarczek; Въглероден Дисулфид; Сероуглерод.
CS_2=76.13
CAS — 75-15-0.
UNII — 5545B99E8.

Description. Carbon disulfide is a clear, colourless, volatile, flammable liquid with a chloroform-like odour. Commercial grades have an unpleasant odour described by some as being reminiscent of decaying radishes. Wt per mL about 1.26 g. B.p. about 46 degrees. Store in airtight containers.

Stability. The vapour of carbon disulfide when mixed with air in the proportions of 1 to 50% is highly explosive.

Uses

Carbon disulfide is used as an industrial solvent and has been used, in the vapour form, as an insecticide.

Adverse Effects, Treatment, and Precautions

Carbon disulfide is irritant. Toxic effects may occur as a result of inhalation, ingestion, or absorption through the skin.

Acute poisoning may result in gastrointestinal disturbances and euphoria, followed by CNS depression. Symptoms include headache, dizziness, mood changes, and in severe cases, manic psychoses, delirium, hallucinations, coma, convulsions, and death due to respiratory failure.

Chronic poisoning has been associated with occupational exposure to carbon disulfide vapour for prolonged periods. It is characterised by peripheral neuropathies; CNS effects such as headache, fatigue, insomnia, tremor, emotional lability, extrapyramidal disorders, bipolar disorder, and encephalopathy; gastrointestinal effects including anorexia, dyspepsia, and ulcerative changes; and effects on the eye. Hearing loss due to noise exposure may be exacerbated. Occupational exposure to carbon disulfide has been shown to be associated with an increased incidence of mortality from coronary heart disease. The action of carbon disulfide on endocrine function has resulted in menstrual irregularities, an increased incidence of spontaneous abortions and premature births, loss of libido, sperm abnormalities, and decreased serum-thyroxine concentrations; there is limited evidence of impaired glucose tolerance.

Treatment consists of removal from exposure and general supportive and symptomatic measures. Gastric lavage should be avoided. Adrenaline and other sympathomimetics should also be avoided because of the risk of precipitating cardiac arrhythmias. Peripheral neuropathies may be only slowly reversible.

Reviews of the toxicity of carbon disulfide.

1. WHO. Carbon Disulfide. *Environmental Health Criteria 10.* Geneva: WHO, 1979. Available at: http://www.inchem.org/documents/ehc/ehc/ehc010.htm (accessed 29/06/04)
2. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
3. Health and Safety Executive. Carbon disulphide. *Toxicity Review 3.* London: HMSO,1981.
4. Beauchamp RO, *et al.* A critical review of the literature on carbon disulfide toxicity. *Crit Rev Toxicol* 1983; 11: 169–278.
5. Huang CC. Carbon disulfide neurotoxicity: Taiwan experience. *Acta Neurol Taiwan* 2004; 13: 3–9.

Effects on endocrine function. The effects of exposure to carbon disulfide were studied retrospectively in 265 female workers in the rayon industry exposed for at least 1 year, and 291 non-exposed female workers.[1] Levels of exposure varied over the study period from 0.7 to 30.6 mg/m³. Women exposed to carbon disulfide had a higher risk of menstrual disturbances than non-exposed women. However, there was no difference between the 2 groups in incidence of toxaemia, emesis gravidarum, spontaneous abortion, premature or overdue delivery, or congenital malformation.

1. Zhou SY, *et al.* Effects of occupational exposure to low-level carbon disulfide (CS_2) on menstruation and pregnancy. *Ind Health* 1988; 26: 203–14.

Effects on the heart. An increased incidence of mortality from cardiovascular disease has been found in workers occupationally exposed to carbon disulfide.[1-3] The evidence suggested that the risk decreases after cessation of exposure. However, a critical review[4] found that evidence for an association was mixed and that any effect was likely to be small.

1. Nurminen M, Hernberg S. Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulphide: a 15 year follow up. *Br J Ind Med* 1985; 42: 32–5.
2. Sweetnam PM, *et al.* Exposure to carbon disulphide and ischaemic heart disease in a viscose rayon factory. *Br J Ind Med* 1987; 44: 220–7.
3. MacMahon B, Monson RR. Mortality in the US rayon industry. *J Occup Med* 1988; 30: 698–705.
4. Suisky SL *et al.* Critical review of the epidemiological literature on the potential cardiovascular effects of occupational carbon disulfide exposure. *Int Arch Occup Environ Health* 2002; 75: 365–80.

Handling. Suitable precautions should be taken to avoid skin contact with carbon disulfide as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Carbon disulfide is rapidly absorbed after inhalation and ingestion, and is also absorbed through intact skin. It is excreted unchanged through the lungs and in the urine mainly as metabolites.

Carbon Tetrachloride

Anglies Tetrachloridas; Czterochlorek węgla; Hiiltetrakloridi; Koltetraklorid; Koolstoftetrachloride; Szén-tetraklorid; Tetra; Tetrachloormethaan; Tetrachlormethan; Tétrachlorométhane; Tétrachlorure de carbone; Tetracloreto de carbono; Tetraclorur de carboni; Tetracloruro de carbono; Tetracloruro di carbonio; Tetrahlorogleklis; Tetraklorkulstof; Węgla tetrachlorek; Четырёххлористый Углерод.
Tetrachloromethane.
CCl_4=153.8
CAS — 56-23-5.
UNII — CL2T97X0V0.

Description. Carbon tetrachloride is a clear, colourless, mobile, liquid with a chloroform-like odour. Sp. gr. 1.588 to 1.590. B.p. 76 degrees to 78 degrees. Practically insoluble in water; miscible with alcohol, chloroform, ether, petroleum spirit, and fixed and volatile oils. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Handling. Avoid contact with carbon tetrachloride; the vapour and liquid are poisonous. Care should be taken not to vaporise carbon tetrachloride in the presence of a flame because of the production of harmful gases, mainly phosgene.

Uses

Carbon tetrachloride is used in industry as a solvent and degreaser. It was formerly used in certain types of fire extinguisher and as an industrial and domestic dry cleaner but has been largely replaced for this purpose by less toxic substances. Carbon tetrachloride has also been used for the fumigation of cereals.

Carbon tetrachloride was formerly given orally as an anthelmintic but it has been superseded by equally effective and less toxic drugs.

Adverse Effects

Individual response to carbon tetrachloride varies widely; inhalation or ingestion of a few mL of carbon tetrachloride has proved fatal and its toxicity appears to be increased by alcohol. Poisoning may follow inhalation, ingestion, or topical application but develops more rapidly after inhalation.

Carbon tetrachloride is irritant; repeated application to the skin may result in dermatitis. Aspiration may result in pulmonary oedema.

Adverse effects after acute exposure from any route include gastrointestinal disturbances such as nausea, vomiting, and abdominal pain, and CNS disturbances such as headache, dizziness, and drowsiness, with progression to convulsions, coma, and death from respiratory depression or circulatory collapse. Death may also occur as a result of ventricular arrhythmia. Hepatic and renal cellular necrosis can occur and are associated with free radical production; symptoms usually begin a few days or up to 2 weeks after acute exposure to carbon tetrachloride. Renal damage may present as oliguria, progressing to proteinuria, anuria, weight gain, and oedema. Symptoms of hepatic damage

include anorexia, jaundice, and hepatomegaly. If hepatorenal necrosis is not fatal recovery is eventually complete.

Symptoms of chronic poisoning are similar to those of acute poisoning; in addition, paraesthesias, visual disturbances, anaemia, and aplastic anaemia have occurred. Carcinogenicity has been found in *animals*.

References.
1. Melamed E, Lavy S. Parkinsonism associated with chronic inhalation of carbon tetrachloride. *Lancet* 1977; i: 1015.
2. Johnson BP, *et al.* Cerebellar dysfunction after acute carbon tetrachloride poisoning. *Lancet* 1983; ii: 968.
3. Perez AJ, *et al.* Acute renal failure after topical application of carbon tetrachloride. *Lancet* 1987; i: 515–6.
4. Health and Safety Executive. Carbon tetrachloride, chloroform. *Toxicity Review 23*. London: HMSO,1992.
5. Manno M, Rezzadore M. Critical role of ethanol abuse in carbon tetrachloride poisoning. *Lancet* 1994; 343: 232.
6. WHO. Carbon tetrachloride health and safety guide. *IPCS Health and Safety Guide 108*. Geneva: WHO, 1998. Available at: http://www.inchem.org/documents/hsg/hsg/hsg108.htm (accessed 29/06/04)
7. IARC/WHO. Carbon tetrachloride. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; 71: 401–32. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

Treatment of Adverse Effects

If carbon tetrachloride vapour has been inhaled the patient should be removed to the fresh air. Clothing contaminated by liquid should be removed and the skin washed. If carbon tetrachloride has been ingested activated charcoal may be given.

The usual symptomatic and supportive measures should be instituted. Hepatic and renal function should be monitored closely. Haemodialysis or peritoneal dialysis may be needed if renal function is impaired. Dopamine or noradrenaline may be used cautiously for severe hypotension unresponsive to fluid replacement, but adrenaline may be best avoided because of the risk of precipitating cardiac arrhythmias.

Acetylcysteine (p. 1653.2) may be given to patients recently exposed to carbon tetrachloride in an attempt to prevent or modify hepatic and renal damage.

Pharmacokinetics

Carbon tetrachloride is readily absorbed after inhalation and ingestion. It is also absorbed through the skin. Metabolism to reactive free radicals is thought to account for the hepatorenal toxicity of carbon tetrachloride.

Carbon tetrachloride is slowly excreted from the body via the lungs and the urine.

Carmellose *(rINN)*

Carbossimetilcellulosa; Carboximetilcelulosa; Carboximetilcelulose; Carboximetilcelulozá; Carboxymethylcellulose; Carboxyméthylcellulose; Carmellosum; Carmelosa; CMC; E466; Karboksimetyyliselluloosa; Karboksymetyloceluloza; Karboximetil-celulóz; Karboxymethylcelulóza; Кармеллоза.

CAS — 9000-11-7.
UNII — 05JZI7B19X.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Carmellose). A white or almost white, hygroscopic powder. It swells in water to form a suspension; becomes viscid in sodium hydroxide; practically insoluble in dehydrated alcohol. A 1% solution in water has a pH of 3.5 to 5.0. Store in airtight containers.

USNF 31: (Carmellose). A white, hygroscopic powder. Swells with water to form a suspension. Practically insoluble in ethanol 99.5%. Becomes viscous in a 4% solution of sodium hydroxide. Store in airtight containers.

Carmellose Calcium *(rINNM)*

Calcii Carmellosum; Calcium Carboxymethylcellulose; Carboximetilcelulosa cálcica; Carboxymethylcellulose Calcium; Carmellose Calcique; Carmellose-Calcium; Carmellosum Calcicum; Carmellosum Calcium; Carmelosa cálcica; Karmeliozės kalcio druska; Karmelloosikalsium; Karmelloskalcium; Karmellóz-kalcium; Karmelosa vápenatá sůl; Кальций Кармеллоза.

CAS — 9050-04-8.
UNII — UTY7PDF93L.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Carmellose Calcium). A white or yellowish-white, hygroscopic powder. It swells in water to form a suspension; practically insoluble in alcohol, in acetone, and in toluene. Store in airtight containers.

USNF 31: (Carboxymethylcellulose Calcium). A white to yellowish-white, hygroscopic powder. It swells in water to form a suspension; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. pH of a 1% suspension in water is between 4.5 and 6.0. Store in airtight containers.

Carmellose Sodium *(BAN, rINNM)*

Carboximetilcelulosa sódica; Carboxymethylcellulose Sodium; Carboxymethylcellulosum Natricum; Carmellose Natrium; Carmellose Sodique; Carmellosum Natricum; Carmelosa sódica; Cellulose Gum; E466; Karmeliozės natrio druska; Karmelloosinatrium; Karmellosnatrium; Karmellóz-nátrium; Karmelosa sodná soľ; Karmeloza sodowa; Natrii Carmellosum; SCMC; Sodium Carboxymethylcellulose; Sodium Cellulose Glycollate; Натрий Кармеллоза.

CAS — 9004-32-4.
UNII — K679OBS311.

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

Eur. and *USNF* also include low-substituted carmellose sodium and *USNF* includes enzymatically-hydrolysed carmellose sodium.

USNF also includes Carboxymethylcellulose Sodium 12.

Ph. Eur. 8: (Carmellose Sodium). A white or almost white, hygroscopic granular powder. It has a sodium content of 6.5 to 10.8% calculated on the dry substance. Easily dispersed in water forming colloidal solutions; practically insoluble in dehydrated alcohol, in acetone, in ether, and in toluene. A 1% colloidal solution in water has a pH of 6.0 to 8.0.

Ph. Eur. 8: (Carmellose Sodium, Low-substituted; Carmellosum Natricum, Substitutum Humile). It contains not less than 2.0% and not more than 4.5% of sodium, calculated with reference to the dried substance. A white or almost white powder or short fibres. It swells in water to form a gel; practically insoluble in dehydrated alcohol, in acetone, and in toluene. A 1% suspension in water has a pH of 6.0 to 8.5.

USP 36: (Carboxymethylcellulose Sodium). A white to cream-coloured, hygroscopic powder or granules. It contains not less than 6.5% and not more than 9.5% of sodium, calculated on the dried basis. Easily dispersed in water to form colloidal solutions; insoluble in alcohol, in ether, and in most other organic solvents. pH of a 1% solution in water is between 6.5 and 8.5. Store in airtight containers.

USNF 31: (Low-Substituted Carboxymethylcellulose Sodium). It has a sodium content of 2.0 to 4.5%, calculated on the dried basis. A white or almost white powder or short fibres. Practically insoluble in alcohol, in acetone, and in toluene. It swells in water to form a gel. pH of a 1% suspension in water is between 6.0 and 8.5. Store in airtight containers.

USNF 31: (Enzymatically-Hydrolyzed Carboxymethylcellulose Sodium). The sodium salt of a polycarboxymethyl ether of cellulose, which has been partially hydrolysed by enzymatic treatment with food grade cellulase from *Trichoderma reesei*. White or slightly yellowish or greyish, odourless, slightly hygroscopic granular or fibrous powder. Soluble in water; insoluble in alcohol. pH of a 1% solution in carbon dioxide-free water is 6.0 to 8.5. Store in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

USNF 31: (Carboxymethylcellulose Sodium 12). A colourless or white to off-white, odourless, powder or granules. Water solubility depends on degree of substitution (easily dispersed in water at all temperatures, forming a clear, colloidal solution). Insoluble in alcohol, in acetone, in ether, and in toluene. It has a sodium content of 10.4 to 12.0%, calculated on the dry substance. Store in airtight containers.

Incompatibility. Incompatibilities of carmellose sodium have been reported with strongly acidic solutions, with soluble salts of iron and some other metals, and with xanthan gum.

Croscarmellose Sodium *(USAN)*

Carboximetilcelulosa sódica reticulada; Carmellosum Natricum Conexum; Croscarmellose-Natrium; Croscarmellose sodique; Croscarmelosa sódica; Crosslinked Carboxymethylcellulose Sodium; E468; Kroskarmeliozės natrio druska; Kroskarmelloosi natrium; Kroskarmellosnatrium; Kroskarmelosa sodná sůl; Kroskarmeloza sodowa; Kroszkarmellóz-nátrium; Modified Cellulose Gum; Кроскармеллоза Натрия.

UNII — M28OL1HH48.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Croscarmellose Sodium). A cross-linked polymer of carmellose sodium. A white or greyish-white powder. Practically insoluble in dehydrated alcohol, in acetone, and in toluene. A 1% suspension in water has a pH of 5.0 to 7.0.

USNF 31: (Croscarmellose Sodium). The sodium salt of a cross-linked partly *O*-(carboxymethylated) cellulose. A white, free-flowing powder. Partially soluble in water; insoluble in alcohol, in ether, and in other organic solvents. pH of a dispersion containing 1 g mixed with 100 mL of water for 5 minutes is between 5.0 and 7.0.

Profile

Pharmaceutical uses of carmellose calcium and carmellose sodium include suspending, thickening, and emulsifying agents, disintegrants, binders, and coating agents in tablets. Carmellose sodium is also used as an emulsifier or stabiliser in the food industry. Croscarmellose sodium is used as a tablet disintegrant.

Carmellose sodium is used topically as an ingredient of protective preparations for stoma care, in the management of wounds, and for the mechanical protection of oral and perioral lesions, such as mouth ulceration (p. 1811.2). It is also used, in concentrations of up to 1%, in artificial saliva preparations for the treatment of dry mouth (below), and in eye drops for the management of dry eye (p. 2190.1).

Carmellose sodium given orally absorbs water and acts as a bulk-forming agent; the volume of faeces is increased and peristalsis promoted. It is used in the treatment of constipation (p. 1804.3). Carmellose sodium has been included in preparations to control appetite in the management of obesity (p. 2315.1) but there is little evidence of efficacy. For precautions to be observed with bulk-forming agents, see under Methylcellulose, p. 2198.1.

Dry mouth. Dryness of the mouth (xerostomia) resulting from decreased salivary secretion is often an adverse effect of therapy with drugs such as antimuscarinics, antihistamines, tricyclic antidepressants, and diuretics. Other causes include dehydration, anxiety, Sjögren's syndrome (see Dry Eye, under Uses of Hypromellose, p. 2190.1), and radiotherapy of the head and neck. Dry mouth can cause eating difficulties and lead to oral disease such as candidiasis, dental caries, and bacterial infections.[1-7]

Treatment of dry mouth is mainly symptomatic. Where possible any underlying disorder should be treated first. Frequent sips of fluids may help to relieve dryness. Artificial saliva products may also be beneficial, although again they may need to be used frequently, seldom relieving symptoms for more than 1 to 2 hours. They aim to mimic normal saliva and generally contain viscosity-increasing agents, such as mucins or cellulose derivatives such as carmellose,[8,9] as well as electrolytes, including fluoride. Preparations containing lactoperoxidase and lactoferrin have also been used.[10] Sialogogues may be used in an attempt to stimulate salivation and may be more effective than saliva substitutes where some salivary function remains. Mechanical stimulants such as sugar-free chewing gum may be effective, and citrus or citric acid preparations are also used, although these may damage the teeth due to their low pH. Malic acid has been used similarly.

Systemic therapies may have a role in some patients. These are mainly based on drugs with cholinergic effects, which stimulate the salivary glands. Pilocarpine is used for dry mouth after radiotherapy and may also be effective in Sjögren's syndrome or other causes of dry mouth; benefit has been reported[11] in patients with dry mouth associated with psychoactive medications. Adverse effects, particularly increased sweating, may, however, limit its use.[12] Cevimeline, which is reported to be more specific for the M_1-muscarinic receptor, may be an alternative in patients with Sjögren's syndrome. Other cholinergics that have been used include carbachol and anethole trithione. Acupuncture has also been tried.[13]

For patients at risk of dry mouth due to radiotherapy, preventative measures are important.[14] Salivary gland-sparing radiation techniques have been developed and cytoprotectants, such as amifostine, have also been used.

1. Silvestre-Donat FJ, *et al.* Protocol for the clinical management of dry mouth. *Med Oral* 2004; 9: 276–9.
2. Al-Hashimi I. Xerostomia secondary to Sjögren's syndrome in the elderly: recognition and management. *Drugs Aging* 2005; 22: 887–99.
3. Chambers MS, *et al.* Radiation-induced xerostomia. *Head Neck* 2007; 29: 58–63.
4. Taubert M, *et al.* Dry mouth. *BMJ* 2007; 334: 534.
5. Turner MD, Ship JA. Dry mouth and its effects on the oral health of elderly people. *J Am Dent Assoc* 2007; 138 (suppl): 15S–20S.
6. Fox PC. Xerostomia: recognition and management. *Dent Assist* 2008; 77: 18, 20, 44–8.
7. Visvanathan V, Nix P. Managing the patient presenting with xerostomia: a review. *Int J Clin Pract* 2010; 64: 404–7.
8. Vissink A, *et al.* A clinical comparison between commercially available mucin- and CMC-containing saliva substitutes. *Int J Oral Surg* 1983; 12: 232–8.
9. Duxbury AJ, *et al.* A double-blind cross-over trial of a mucin-containing artificial saliva. *Br Dent J* 1989; 166: 115–20.
10. Gil-Montoya JA, *et al.* Evaluation of the clinical efficacy of a mouthwash and oral gel containing the antimicrobial proteins lactoperoxidase, lysozyme and lactoferrin in elderly patients with dry mouth—a pilot study. *Gerodontology* 2008; 25: 3–9.
11. Masters KJ. Pilocarpine treatment of xerostomia induced by psychoactive medications. *Am J Psychiatry* 2005; 162: 1023.
12. Davies AN, Shorthose K. Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 23/06/08).
13. Meidell L, Holritz Rasmussen B. Acupuncture as an optional treatment for hospice patients with xerostomia: an intervention study. *Int J Palliat Nurs* 2009; 15: 12–20.
14. Dirix P, *et al.* Radiation-induced xerostomia in patients with head and neck cancer: a literature review. *Cancer* 2006; 107: 2525–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aqua Lent Lubricante; Aquacel; Audic; Comfeel Plus; Comfeel; Natura Fresh; Nu-Derm Hidrocoloide; Refresh Liquigel; Refresh Tears; *Austral.*: Cellufresh; Celluvisc; Refresh Contacts; Refresh Liquigel; Refresh Plus; Refresh Tears Plus; TheraTears; *Belg.*: Aquacel; Comfeel; Gelilact†; *Braz.*: Cellufresh; Ecofilm; Fresh Tears; Lacrifilm; Plenigell; Salivan; *Canad.*: Aquacel; Refresh Celluvisc; Refresh Contacts; Refresh Liquigel; Refresh Plus; Refresh Tears; TheraTears; *Chile*: Refresh Liquigel; Refresh Tears; *China*: Celluvisc (福莱威); Kai Shi (开仕); Refresh Plus (瑞新); *Cz.*: Cellufluid; *Denm.*: Cellufluid; Celluvisc; *Fin.*: Cellufluid; Celluvisc; *Fr.*: Aquacel; Blatain; Celluvisc; Clip Ampoules†; Clip Brulures†; Comfeel; Hydrocoll; Physiotulle; Urgomed; Urgotul; *Ger.*: Algoplaque; Alione; Cellufresh; Cellumed; Celluvisc; Comfeel Plus Transparenter; DracoHydro; Physiotulle; UrgoCell Adhesive; UrgoCell Contact; UrgoCell Heel Contact; Urgocell Lite; UrgoCell Non Adhesive; Urgotul comfort; Urgotul Duo; Urgotul Lite Border; Urgotul Soft; Urgotul; *Gr.*: Cellufluid; Celluvisc; Refresh Plus; *Hong Kong*: Refresh; *India*: Add Tears; Aftee DPS; Celluvisc; E-Moist; Eco Tears; Flogel; I-Lax; Irivisc; Lacrimos; Lubrex; Max-Moist; MCM-Tear; Mep-Con; Moitz; Nistear; Oass; Optive; *Irl.*: Celluvisc; *Israel*: Celluvisc†; Refresh Tears; TheraTears; *Ital.*: Cellufresh; Celluvisc; Lacrilens; *Malaysia*: Celluvisc; Clarastill; Refresh Liquigel; Refresh Plus; Refresh Tears; *Mex.*: Acutears; Novafix Ultra Puerte; Refresh Liquigel; Refresh Tears; *Neth.*: Cellufluid; Celluvisc; *Norw.*: Celluvisc; *NZ*: Refresh Tears Plus; *Philipp.*: Cellufresh; Celluvisc; *Port.*: Cellufluid; Celluvisc; *S.Afr.*: Aquacel†; Cellufresh; Celluvisc; Comfeel; Intrasite; Refresh Liquigel; Refresh Tears; *Singapore*: Celluvisc; Optive; Refresh Contacts; Refresh Liquigel; Refresh Plus; Refresh Tears; *Spain*: Cellufresh; Celluvisc†; Viscofresh; *Swed.*: Cellufluid; Celluvisc; *Switz.*: Cellufluid; Celluvisc; *Thai.*: Cellufresh; Celluvisc; *Turk.*: Cellufresh; Refresh Liquigel; Refresh Tears Lubricant; *UK*: Aquacel; Carmize; Celluvisc; Comfeel; Intrasite; Murine Contacts; Physiotulle; *USA*: Celluvisc; Clear Eyes for Dry Eyes; Optive; Refresh Liquigel; Refresh Plus; Refresh Tears; Tears Again; TheraTears; *Venez.*: Refresh Liquigel; Refresh Tears.

Multi-ingredient Preparations. *Arg.*: Comfeel Purilon; Comfeel SeaSorb; Humectante Bucal; Mucobase; Optive; Purilon†; SeaSorb†; *Austral.*: Aquae; Optive; Orabase; SoloSite; Stomahesive; *Austria*: Glandosane; Sialin; *Belg.*: Aquacel-Ag; *Braz.*: Chofraninа†; Optive; Sepraflim; *Canad.*: Carboflex; Clear Eyes for Dry Eyes; Genteal Geldrops; Moi-Stir; Orabase; Orahesive; Tegasorb†; *Chile*: Delgadol Fibra; K.C.M.C; Novafix Extra Puerte; Novafix Ultra Puerte; Optive; Reducform-F; *Cz.*: Spofax; *Fr.*: Altreet Ag; Aquacel Ag; Artisial; Biatain Ag; Cellosorb†; Clip Hemo†; Intrasite; Melgisorb; Purilon; Release Ag†; SeaSorb; Sorbalgon Plus; Urgosorb; Urgotul S.Ag; *Ger.*: Comfeel Plus; DracoAlgin; Glandosane; GoTa-Derm; Lary-Phary; Melgisorb Ag; Optive; Physiotulle-Ag; Purilon; Recatol Algin; SeaSorb Soft; SeaSorb-Ag; UrgoCell Silver; UrgoCell Start; Urgoclean Kompresse; UrgoSTART; Urgotul S.Ag; Urgotul Silver; Xerotin; *Hong Kong*: Glandosane; Optive; Salivart†; *India*: Alupectin DGL; Alupectin; Aqwet; Bioffin; Coolpep; Digene; Entagene; Pittydent; Laxit; Novagel; *Irl.*: Orabase†; *Israel*: Optive; *Ital.*: Aquacel Ag; *Malaysia*: Sepraflim; *Mex.*: Optive; *NZ*: Orabase; Stomahesive; *Philipp.*: Optive; *Port.*: Glandosane†; *S.Afr.*: Granuflex; Granugel; Orabase†; *Singapore*: Sepraflim; *Spain*: Laxvital†; *Switz.*: Glandosane; Optive; *Thai.*: Bisolax; Emulax; Glandosane; Optive; *UK*: Aquacel Ag; Comfeel Plus; Glandosane; Luborant†; Murine Dry & Tired Eyes; Optive; Orabase; Orahesive; Physiotulle-Ag; SeaSorb Soft; Sepraflim; Stomahesive; Xerotin; *Ukr.*: Optive (Оптив); *USA*: Entertainer's Secret; Moi-Stir; Pretts Diet Aid; Salivart; Sepraflim; Surgel; *Venez.*: Klincosal; Novafix; Polantac.

Pharmacopoeial Preparations

BP 2014: Carmellose Sodium Eye Drops;
USP 36: Carboxymethylcellulose Sodium Paste; Carboxymethylcellulose Sodium Tablets.

Carmine

Carmim; Carmin; Carminio; CI Natural Red 4; Cochineal Carmine; Colour Index No. 75470; E120; Karmijn; Karmin; Karmín; Karminas; Kārminvörös; Rouge cochenille; Кармин.
CAS — 1390-65-4.

Uses

Carmine is an aluminium lake of the colouring matter of cochineal (p. 2179.2). It contains carminic acid, an anthraquinone glycoside. Unless precautions are taken during manufacture and transport to prevent contamination, carmine may be infected with salmonella microorganisms.

Carmine and some of its salts are used as colouring agents in medicines, foodstuffs, and cosmetics.

Carmine passes through the gastrointestinal tract unchanged and has been used as a faecal 'marker'.

Adverse Effects

Hypersensitivity. By February 2004 the FDA was aware of 35 cases of hypersensitivity to carmine, carminic acid, or cochineal extract published in the scientific and medical literature and/or reported directly to the FDA. Hypersensitivity reactions to carmine, carminic acid, or cochineal extract included contact dermatitis (4 cases), urticaria/angioedema (9), occupational asthma (10), and systemic anaphylaxis (12). In more than half of these reports, there was evidence of an IgE-mediated diagnostic response. The adverse effects included allergic reactions to foods containing carmine and cochineal extract, occupational asthma from exposure to carmine, and allergic reactions to topically applied cosmetics containing carmine.

The FDA concluded that carmine and cochineal extract may cause potentially severe allergic responses and proposed that food and cosmetic labelling be enhanced; a declaration of inactive ingredients in drugs was already in force.[1] From January 2011, the FDA will require that the presence of cochineal extract or carmine must be declared on the product label of foods and cosmetics.[2]

1. FDA. Food, drug, and cosmetic labelling: cochineal extract and carmine declaration. Proposed rule. *Fed Regist* 2006; 71: 4839–51. Available at: http://edocket.access.gpo.gov/2006/pdf/E6-1104.pdf (accessed 23/08/10)
2. FDA. Food, drug, and cosmetic labelling: cochineal extract and carmine declaration. Final rule. *Fed Regist* 2009; 74: 207–17. Available at: http://edocket.access.gpo.gov/2009/pdf/E8-31253.pdf (accessed 23/08/10)

Carmoisine

Atsorubiini; Azorrubina; Azorubin; Azorubine; Carmoisina; CI Food Red 3; Colour Index No. 14720; E122; Кармуазин.
It consists mainly of disodium 4-hydroxy-3-(4-sulphonato-1-naphthylazo)naphthalene-1-sulphonate.
$C_{20}H_{12}N_2Na_2O_7S_2$=502.4
CAS — 3567-69-9.
UNII — DR4641L47F.

Profile

Carmoisine is a synthetic azo dye used as a colouring agent in foods, medicines, and cosmetics. It has also been investigated clinically as a stain, to aid visualisation of malignant neoplasms of the skin during surgery.

Carnauba Wax

Brazil Wax; Caranda Wax; Carnauba, cire de; Carnaubawachs; Carnaubawas; Cera carnaúba; Cera Copernicíae; Cera de carnauba; E903; Karnaúba pálmaviasz; Karnaubavaha; Karnaubavax; Karnaubo vaškas; Vosk karnaubský; Карнаубский Воск.
CAS — 8015-86-9.
UNII — R12CBM0EIZ.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Carnauba Wax). It is obtained from the leaves of *Copernicia cerifera*. Pale yellow or yellow powder, flakes, or hard masses. It has a relative density of about 0.97. M.p. 80 degrees to 88 degrees. Practically insoluble in water and in alcohol; soluble on heating in ethyl acetate and in xylene. Protect from light.

USNF 31: (Carnauba Wax). It is obtained from the leaves of *Copernicia cerifera* (Palmae). A light brown to pale yellow, moderately coarse powder or flakes, possessing a characteristic bland odour, and free from rancidity. Sp. gr. about 0.99. M.p. 80 degrees to 86 degrees. Insoluble in water; slightly soluble in boiling alcohol; soluble in warm chloroform and in warm toluene; freely soluble in warm benzene.

Profile

Carnauba wax is used in pharmacy as a coating agent. Its use is also permitted in certain foods. Various types and grades are used industrially in the manufacture of polishes.

Carotenoids

Carotenoïden; Carotenoides; Caroténoïdes; Carotenoidi; Carotinoide; Karatenoidler; Karotenoider; Karotenoidit; Karotenoidy; Karotinoidid; Каротиноиды.
CAS — 36-88-4.

Profile

Carotenoids are tetraterpenoid compounds that occur naturally as pigments in plants and algae. They can be divided into carotenes and xanthophylls (which also contain oxygen). Some are used as colouring agents in foods, drugs, and cosmetics, while others are also used for their nutritional properties. Some carotenoids are metabolised in the body to retinoids and have vitamin A activity. Carotenoids used as colourings include bixin and norbixin (derivatives of annatto, p. 2169.1), capsanthin and capsorubin (derivatives of paprika, E160c), apocarotenal (p. 2169.2), astaxanthin (p. 2170.1), canthaxanthin (p. 2173.2), and citranaxanthin (p. 2179.2); those that have been used therapeutically include carotene (see Betacarotene, p. 2051.1), lutein (p. 2079.2), lycopene (p. 2546.2), and zeaxanthin (p. 2125.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Betarene†; Eyegold†.

Multi-ingredient Preparations. *India*: GB-Lex; Kefive Plus; Lycogold; Macuchek; Macugold; Menofit; Multivite Gold; Multivite Vision; Multivite Woman; Multivite-FM Omega; Ocufree; *Mex.*: Optima IFX; *Thai.*: Diavit; *Ukr.*: Perfectil Plus (Перфектил Плюс); Wellman (Велмен).

Carrageenan

Carrageen; Carrageenanum; Carrageenin; Carragenano; Carragenatos; Carragenina; Carragenos; Carraghénanes; Carraghénates; Carraghenina; Chondrus Extract; E407; Irish Moss Extract; Karagenan; Karragén; Karragenan; Каррагинан.
CAS — 9000-07-1 (carrageenan); 11114-20-8 (κ-carrageenan); 9064-57-7 (λ-carrageenan).
UNII — 5C69YCD2YJ.

Pharmacopoeias. In *Eur.* (see p. vii) and *Fr.* Also in *USNF* which also includes the related substance Galageenan.

Ph. Eur. 8: (Carrageenan). Polysaccharides obtained by extraction with water or aqueous alkali from some members of the class Rhodophyceae (red seaweeds). It consists chiefly of a mixture of the calcium, magnesium, potassium, and sodium salts of the sulfate esters of D-galactose and 3,6-anhydro-D-galactose copolymers. The prevalent copolymers are κ-carrageenan, ι-carrageenan, and λ-carrageenan.

A yellowish, brownish, or white or almost white powder. Soluble in water giving a viscous or colloidal solution; insoluble in organic solvents.

USNF 31: (Carrageenan). The hydrocolloid obtained by extraction with water or aqueous alkali from some members of the class Rhodophyceae (red seaweeds). It consists chiefly of a mixture of the ammonium, calcium, magnesium, potassium, and sodium sulfate esters of galactose and 3,6-anhydrogalactose copolymers. The prevalent copolymers in the hydrocolloids are κ-carrageenan, ι-carrageenan, and λ-carrageenan.

A yellowish or tan to white, coarse to fine, practically odourless, powder. Soluble in water at 80 degrees forming a viscous, clear or slightly opalescent solution that flows readily. It disperses more readily in water if first moistened with alcohol, with glycerol, or with a saturated solution of glucose in water. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

USNF 31: (Galageenan). The hydrocolloid obtained by extraction with water or aqueous alkali from the red seaweed *Eucheuma gelatinae* (Rhodophyceae). Galageenan consists chiefly of potassium, sodium, calcium, magnesium, and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers. These hexoses are alternately linked in α-1,3 and β-1,4 in the polymer. The ester sulfate content ranges from 8 to 18%. In addition, it contains inorganic salts that originate from the seaweed and from the process of recovery from the extract. Galageenan is recovered by alcohol precipitation or by freezing and pressing. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Profile

Carrageenans are a family of polysaccharides containing different copolymers of D-galactose and 3,6-anhydro-D-galactose. They are obtained from various red seaweeds. Carrageenans are used in pharmaceutical manufacturing and the food industry as suspending and gelling agents. Galageenan, a carrageenan also obtained from a red seaweed (*Eucheuma gelatinae*) is used similarly.

Carrageenan has been used as a bulk-forming laxative to treat constipation; for precautions to be observed with bulk-forming laxatives, see under Methylcellulose, p. 2198.1. Carrageenan is also included in topical preparations for the symptomatic relief of anorectal disorders. A gel containing carrageenan has been investigated as a topical microbicide.

A degraded form of carrageenan was formerly used in gastrointestinal disorders but it was associated with lesions in *animals* and is no longer used.

Irish moss (*Chondrus crispus*), a source of carrageenan, is used in herbal medicine.

Refined non-degraded carrageenan and furcellaran, a similar extract from Rhodophyceae that is included in the

specifications for food-grade carrageenan, have generally been considered safe for use as food additives, although this may not be the case with degraded and 'semi-refined' forms.[1,2] However, in the UK the Food Advisory Committee has recommended that carrageenan should not be permitted as an additive for infant formulas because of the possibility of immunological consequences after absorption from the immature gut.[3] Carrageenans affect the immune system of experimental *animals* after parenteral or oral use, and small amounts of food-grade carrageenan cross the intestinal epithelium in *rats* and are taken up by gut-associated lymphoid tissue.[4]

1. FAO/WHO. Evaluation of certain food additives and contaminants: twenty-eighth report of the Joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 710* 1984.
2. Cohen SM, Ito N. A critical review of the toxicological effects of carrageenan and processed eucheuma seaweed on the gastrointestinal tract. *Crit Rev Toxicol* 2002; 32: 413–44.
3. MAFF. Food Advisory Committee: report on the review of the use of additives in foods specially prepared for infants and young children. PdAC/REP/12. London: HMSO, 1992.
4. MAFF. Food Advisory Committee: report on the review of the emulsifiers and stabilisers in food regulations. PdAC/REP/11. London: HMSO, 1992.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Bonningtons Irish Moss; Calporo†; *China*: Titanoreine (太宁); Titanoreine (太宁); *Fr.*: Elgydium Blancheur; Herpclair; Titanoreine Lidocaine; Titanoreine; *Ger.*: Saseem; Silence; *Ital.*: Emoform Alifresh; Resource Gelificata†; *NZ*: Bonningtons Irish Moss; *Singapore*: Silence; *Spain*: Titanorein; *Switz.*: Silence†; Silence; *UK*: Fam-Lax Senna; *USA*: Numoisyn.

Cellulose

Cellulloze; Cellulosa; Celulóz; Celulosa; Cellulose; Celuloză; Celúloza; Celulóza; Selluloosa; Sellulósi; Selulosa; Selūloz; Tselluloos; Zellulose; Ценулоза; Целлюлоза.

UNII — SMD1X3XO9M.

Description. Cellulose is an unbranched polysaccharide polymer consisting of 1,4-β-linked glucopyranose units. It is the chief constituent of fibrous plant material.

Dispersible Cellulose *(BAN)*

Cellulose microcristalline et carmellose sodique; Cellulose, Mikrokristalline und Carmellose-Natrium; Cellulosum microcristallinum et carmellosum natricum; Celulosa dispersable; Microcrystalline Cellulose and Carboxymethylcellulose Sodium; Microcrystalline Cellulose and Carmellose Sodium; Диспергируемая Целлюлоза.

Pharmacopoeias. In *Br.* and *Eur.* (see p. vii). Also in *USNF.*

BP 2014: (Dispersible Cellulose). An odourless or almost odourless, white or off-white, coarse or fine powder consisting of a colloid-forming attrited mixture of microcrystalline cellulose and carmellose sodium. Disperses in water to produce a white, opaque dispersion or gel; practically insoluble in organic solvents and in dilute acids. Store at a temperature between 8 degrees and 15 degrees.

Ph. Eur. 8: (Microcrystalline Cellulose and Carmellose Sodium). A colloid-forming, powdered mixture of microcrystalline cellulose with 5 to 22% of carmellose sodium. It contains 75 to 125% of the nominal amount of carmellose sodium, calculated with reference to the dried substance. A white or off-white, coarse or fine powder. Dispersible in water producing a white, opaque colloidal dispersion; practically insoluble in organic solvents and in dilute acids. pH of a 2% dispersion in water is 6 to 8.

USNF 31: (Microcrystalline Cellulose and Carboxymethylcellulose Sodium). A colloid-forming, attrited mixture of microcrystalline cellulose and carmellose sodium. A white to off-white, odourless, coarse to fine, powder. It swells in water, producing, when dispersed, a white, opaque dispersion or gel; insoluble in organic solvents and in dilute acids. Store in airtight containers in a dry place, and at a temperature not exceeding 40 degrees.

Microcrystalline Cellulose

Cellulloze, mikrokristalline; Cellulosa Microgranulare; Cellulosa, mikrokristallin; Cellulose Gel; Cellulose microcristalline; Cellulosum Microcristallinum; Cellulosum Microcrystallinum; Cellulosum Microristallinum; Celulosa microcristalina; Celulosa mikrokrystalická; Celuloza mikrokrystaliczna; Crystalline Cellulose; E460; Gel de celulosa; Mikrokristályos cellulóz; Selluloosa, mikrokiteinen; Целлюлоза Микрокристаллическая.

CAS — 9004-34-6.

UNII — OP1R32D61U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

USNF also includes silicified microcrystalline cellulose.

Ph. Eur. 8: (Cellulose, Microcrystalline). A purified, partly depolymerised cellulose, prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant materials, with mineral acids. It is a white or almost white, fine or granular powder. Practically insoluble in water, in dehydrated alcohol, in acetone, in toluene, in dilute acids, and in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid obtained from a 12.5% mixture in water after 20 minutes of shaking is 5.0 to 7.5.

USNF 31: (Microcrystalline Cellulose). A purified, partially depolymerised cellulose, prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant material, with mineral acids. It is a fine, white or almost white powder consisting of free-flowing, nonfibrous particles. Insoluble in water, in dilute acids, and in most organic solvents; practically insoluble in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid obtained from a 12.5% mixture in water after 20 minutes of shaking is between 5.0 and 7.5. Store in airtight containers.

USNF 31: (Silicified Microcrystalline Cellulose). A white or almost white, fine powder. Practically insoluble in water, in alcohol, in acetone, in diluted acid, and in toluene; slightly soluble in sodium hydroxide solution (1 in 20). The pH of the supernatant obtained from a 12.5% mixture in water after 20 minutes of shaking is between 5.0 and 7.5. Store in airtight containers.

Powdered Cellulose

Celluloses miltelfai; Cellulosapulver; Cellulose en poudre; Cellulose Powder; Cellulosi Pulvis; Celulózpor; Celulosa en polvo; Celulosový prášek; E460; Selluloosajauhe; Целлюлоза В Порошке.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Cellulose, Powdered). A purified mechanically disintegrated cellulose prepared from alpha-cellulose obtained as a pulp from fibrous plant materials. It is a white or almost white, fine or granular powder. Practically insoluble in water, in dehydrated alcohol, in acetone, in toluene, in most organic solvents, and in dilute acids; slightly soluble in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid of an 11.1% mixture in water is between 5.0 and 7.5 one hour after preparation.

USNF 31: (Powdered Cellulose). A purified, mechanically disintegrated cellulose prepared by processing alpha-cellulose obtained as a pulp from fibrous plant materials. It is a white or almost white powder. Exhibits degrees of fineness ranging from a free-flowing, dense powder to a coarse, fluffy, nonflowing material. Insoluble in water, in nearly all organic solvents, and in dilute acids; slightly soluble in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid of an 11.1% mixture in water is between 5.0 and 7.5 one hour after preparation. Store in airtight containers.

Profile

Powdered cellulose and microcrystalline cellulose are used in pharmaceutical manufacturing as tablet binders and disintegrants and as capsule and tablet diluents. These two forms of cellulose are also used in the food industry. Dispersible cellulose (which also contains some carmellose sodium) forms a thixotropic gel with water and is used pharmaceutically as a suspending and thickening agent.

Various forms of cellulose have been included in preparations used in the management of constipation and obesity. Cellulose is also used in adsorbent powder preparations used for skin disorders including hyperhidrosis.

Derivatives of cellulose, including cellulose esters (below) and cellulose ethers (see Methylcellulose, p. 2197.3), are also widely used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Nasaleze; *Ital.*: Fibrasan†; *UK*: Allergy Defence; Sterigel; *USA*: Unifiber.

Multi-ingredient Preparations. *Arg.*: ZeaSorb; *Austral.*: ZeaSorb†; *Canad.*: ZeaSorb; *Fr.*: Gelopectose; Hydrodean; ZeaSorb; *India*: Mezol; *Irl.*: ZeaSorb; *Thai.*: ZeaSorb†; *UK*: ZeaSorb.

Cellulose Esters

Cellaburate *(rINN)*

Celaburát; Celaburato; Celluliozes acetatas-butiratas; Cellaburatum; Cellulosaacetatbutyrat; Cellulose Acetate Butanoate; Cellulose Acetate Butyrate; Cellulose, acétate butyrate de; Celluloseacetatbutyrat; Cellulosi acetas butyras; Cellulóz-acetát-butirát; Selluloosa-asetaattibutyraatti; Целлабурат.

CAS — 9004-36-8.

NOTE. Cabufocon A and Cabufocon B are both USAN for cellulose acetate butyrate.

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

Ph. Eur. 8: (Cellulose Acetate Butyrate). A partly or completely *O*-acetylated and *O*-butyrated cellulose containing not less than 2.0% and not more than 30.0% of acetyl groups and not less than 16.0% and not more than 53.0% of butyryl groups, calculated with reference to the dried substance. A white, yellowish-white, or greyish-white, slightly hygroscopic, powder or granules. Practically insoluble in water and in alcohol; soluble in acetone, in formic acid, and in a mixture of equal volumes of methyl alcohol and dichloromethane. Store in airtight containers.

Cellacefate *(BAN, rINN)*

Acetato ftalato de celulosa; CAP; Celacefat; Celacefát; Celacefato; Celluliozes acetatas-ftalatas; Cellacéfate; Cellacefatum; Cellacephate; Cellulosaacetatftalat; Cellulose, acétate phtalate de; Cellulose Acetate Phthalate; Celluloseacetatphthalat; Cellulosi acetas phthalas; Cellulosum Acetylphthalicum; Celulóz-acetát-ftalát; Celophthalum; Selluloosa-asetaattiftalaatti; Целлацефат.

CAS — 9004-38-0.

UNII — F2O5O2O19F.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Cellulose Acetate Phthalate; Cellacefate BP 2014). Cellulose in which some of the hydroxyl groups are acetylated (21.5 to 26.0%) and some are phthalylated (30.0 to 36.0%), both calculated with reference to the anhydrous, acid-free substance.

A hygroscopic, white or almost white, free-flowing powder or colourless flakes. Practically insoluble in water, in dehydrated alcohol, and in dichloromethane; freely soluble in acetone; soluble in diethylene glycol; it dissolves in dilute solutions of alkalis. Store in airtight containers.

USNF 31: (Cellacefate). A reaction product of phthalic anhydride and a partial acetate ester of cellulose. It contains 21.5 to 26.0% of acetyl groups, and 30.0 to 36.0% of phthalyl (*o*-carboxy-benzoyl) groups, calculated on the anhydrous, acid-free basis. A white, free-flowing powder that may have a slight odour of acetic acid. Insoluble in water and in alcohol; soluble in acetone and in dioxan. Store in airtight containers.

Cellulose Acetate

Acetát celulosy; Acetyl cellulose; Acetylcellulose; Celluliozes acetatas; Cellulosaacetát; Cellulose, acétate de; Cellulosaacetat; Cellulosi Acetas; Celulóz-acetát; Celulozy octan; Selluloosa-asetaatti; Ацетилцеллюлоза.

CAS — 9004-35-7 (cellulose acetate); 9035-69-2 (cellulose diacetate); 9012-09-3 (Cellulose triacetate).

UNII — 3J2P07GVB6.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Cellulose Acetate). Partly or completely *O*-acetylated cellulose. A white, yellowish-white, or greyish-white, hygroscopic powder or granules. Practically insoluble in water and in alcohol; soluble in acetone, in formic acid, and in a mixture of equal volumes of methyl alcohol and dichloromethane.

USNF 31: (Cellulose Acetate). A partially or completely acetylated cellulose. It contains not less than 29.0% and not more than 44.8%, by weight, of acetyl groups, calculated on the dried basis. A fine, white powder or free-flowing pellets. Available in a range of viscosities and acetyl contents. High viscosity, which reflects high molecular weight, decreases solubility slightly. High acetyl content cellulose acetates generally have more limited solubility in commonly used organic solvents than low acetyl content cellulose acetates, but are more soluble in dichloromethane. All acetyl content cellulose acetates are insoluble in water and in alcohol; soluble in dioxane and in dimethylformamide. Store in airtight containers.

Profile

Cellulose esters are derivatives of cellulose (above) in which some or all of the hydroxyl groups are esterified. Organic cellulose esters such as cellulose acetate and the mixed esters cellaburate and cellacefate are used as tablet and capsule coatings and in the formulation of modified-release and transdermal drug delivery systems. Cellacefate is unaffected by immersion in acid media in the stomach but softens and swells in intestinal fluid. It is used as an enteric-coating material for tablets and capsules, usually with a plasticiser. Films of cellacefate are reported to be permeable to some ionic substances such as ammonium chloride and potassium iodide, and such substances require a sealing coat.

Cellulose esters have many industrial applications, particularly in plastics. Cellulose acetate film has been used in the photographic and cinematographic industries, and cellulose acetate fibre is used in the textiles industry.

Cellulose esters including cellacefate and cellulose sulfate, an inorganic cellulose ester, have been tried as vaginal microbicides but results have been disappointing (see HIV Infection and AIDS, below).

HIV infection and AIDS. Both cellulose sulfate and cellacefate have shown activity against HIV *in vitro* and in *animal* models but studies in humans have been less promising. A study[1] using a cellulose sulfate vaginal microbicidal gel for the prevention of HIV infection (p. 959.1) was terminated early because of evidence that suggested that it might in fact increase the risk of acquiring the virus.

1. Van Damme L, *et al.* CS Study Group. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. *N Engl J Med* 2008; 359: 463–72.

Ceratonia

Carob Bean Gum; Carob Gum; Cerat.; Ceratonia Gum; E410; Farine de Caroube; Fruktkärnmjöl; Goma de garrofín; Goma de semillas de algarrobo; Gomme de Caroube; Guma z nasion Carobe; Locust Bean Gum; Saldžiosios ceratonijos lipai; Szentjánoskenyér-liszt; Камедь Рожкового Дерева; Цератония.

CAS — 9000-40-2.
ATC — A07XA02.
ATC Vet — QA07XA02.
*ATC Herb — HA04WB5002 (*Ceratonia siliqua*: fruit); HA07BW5001 (*Ceratonia siliqua*: fruit); HA04WB5001 (*Ceratonia siliqua*: endosperm).*
UNII — V4716MY704.

Profile

Ceratonia consists of the endosperms separated from the seeds of the locust bean tree, *Ceratonia siliqua* (Leguminosae). It is used as a thickening agent and stabiliser in the food industry.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Irl.*: Carobel; *Switz.*: Nestargel†; *UK*: Carobel; Nestargel.

Multi-ingredient Preparations. *Austria*: China-Eisenwein†; *Fr.*: Gumilk; *Indon.*: Polysilane; *Singapore*: Bios Life.

Cetostearyl Alcohol

Alcohol cetoestearílico; Alcohol cetylicus et stearylicus; Alcohol Cetylstearylicus; Alcool Cétostearilico; Alkohol cetostearylowy; Cetearyl Alcohol; Cetil-sztearil-alkohol; Cetostearilo alkoholis; Cetostearyl Alc.; Cetostearylalkohol; Cétostéarylique, alcool; Cetylstearylalkohol; Setostearyylialkoholi; Цетостеариловый Спирт.

CAS — 8005-44-5; 67762-27-0.
UNII — 2DMT128M1S.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Eur. also includes Cetostearyl Alcohol, Emulsifying, but this is described under Emulsifying Waxes (p. 2184.1).

Ph. Eur. 8: (Cetostearyl Alcohol). A mixture of solid aliphatic alcohols, mainly stearyl alcohol and cetyl alcohol. It contains not less than 90% of stearyl plus cetyl alcohols and not less than 40% of stearyl alcohol. A white or pale yellow wax-like mass, plates, flakes, or granules. M.p. 49 degrees to 56 degrees. Practically insoluble in water; soluble in alcohol and in petroleum spirit. When melted, it is miscible with fatty oils, with liquid paraffin, and with melted wool fat.

USNF 31: (Cetostearyl Alcohol). It contains not less than 40% of stearyl alcohol ($C_{18}H_{38}O$ = 270.5) and the sum of the stearyl alcohol content and the cetyl alcohol ($C_{16}H_{34}O$ = 242.4) content is not less than 90%. Unctuous, white flakes or granules, having a faint, characteristic odour. M.p. 48 degrees to 55 degrees. Insoluble in water; soluble in alcohol and in ether.

Uses

Cetostearyl alcohol is used in creams, ointments, and other topical preparations as a stiffening agent and emulsion stabiliser. It is also used to improve the emollient properties of paraffin ointments. Emulsifying forms are prepared by adding a suitable surfactant and are described under Emulsifying Waxes (p. 2184.1). Cetostearyl alcohol is also used in the formulation of modified-release oral preparations.

Adverse Effects

Cetostearyl alcohol can cause hypersensitivity.

Hypersensitivity. Sensitivity reactions to cetostearyl alcohol in topical preparations have been reported rarely.[1-3]

1. Pecegueiro M, *et al.* Contact dermatitis to Hirudoid cream. *Contact Dermatitis* 1987; 17: 290–3.
2. Marston S. Contact dermatitis from cetostearyl alcohol in hydrocortisone butyrate lipocream, and from lanolin. *Contact Dermatitis* 1991; 24: 372.
3. Rademaker M, *et al.* Contact dermatitis from cetostearyl alcohol. *Australas J Dermatol* 1997; 38: 220–1.

Preparations

Pharmacopoeial Preparations
BP 2014: Cetomacrogol Emulsifying Wax; Cetrimide Emulsifying Ointment; Emulsifying Wax;
USNF 31: Emulsifying Wax.

Cetyl Alcohol

Alcohol cetílico; Alcohol cetylicus; Alcohol Hexadecílico; Álcool Cetílico; Alkohol cetylowy; Cetanol; Cetil-alkohol; Cetilo alkoholis; Cetylalkohol; Cétylique, alcool; Ethal; Ethol; 1-Hexadecanol; Hexadecan-1-ol; Hexadecyl Alcohol; *n*-Hexadecyl Alcohol; Palmityl Alcohol; Setyylialkoholi; Цетиловый Спирт.

$C_{16}H_{34}O$=242.4
CAS — 36653-82-4; 124-29-8.
UNII — 936JST6JCN.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Cetyl Alcohol). A mixture of solid alcohols, mainly cetyl alcohol, of animal or vegetable origin. It occurs as a white or almost white, unctuous mass, powder, flakes, or granules. M.p. 46 degrees to 52 degrees. Practically insoluble in water; freely to sparingly soluble in alcohol; miscible when melted with animal and vegetable oils, with liquid paraffin, and with melted wool fat.

USNF 31: (Cetyl Alcohol). A mixture containing not less than 90% of cetyl alcohol the remainder consisting chiefly of related alcohols. White unctuous flakes, cubes, granules, or castings, with a faint characteristic odour. M.p. 45 degrees to 50 degrees. Insoluble in water; soluble in alcohol and in ether, the solubility increasing with increasing temperature.

Uses

Cetyl alcohol is used in topical preparations for its emollient, water absorptive, stiffening, and weak emulsifying properties. It may be incorporated into suppositories to raise the melting-point and may be used in the coating of modified-release solid dose forms. It is also used in cosmetics.

Adverse Effects

Cetyl alcohol can cause hypersensitivity.

Hypersensitivity. Hypersensitivity reactions have occasionally been attributed to the presence of cetyl alcohol in topical preparations.[1-4] One report suggested that minor impurities in the cetyl alcohol may be responsible.[1]

1. Komamura H, *et al.* A case of contact dermatitis due to impurities of cetyl alcohol. *Contact Dermatitis* 1997; 36: 44–6.
2. Oiso N, *et al.* Concomitant allergic reaction to cetyl alcohol and crotamiton. *Contact Dermatitis* 2003; 49: 261.
3. Soga F, *et al.* Contact dermatitis due to lanoconazole, cetyl alcohol and diethyl sebacate in lanoconazole cream. *Contact Dermatitis* 2004; 50: 49–50.
4. Klec-Swierczynska M, *et al.* Photoallergic and allergic reaction to 2-hydroxy-4-methoxybenzophenone (sunscreen) and allergy to cetyl alcohol in cosmetic cream. *Contact Dermatitis* 2005; 53: 170–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lactopan; *India*: Nosoap.

Multi-ingredient Preparations. *Arg.*: Caien†; *Hong Kong*: Ego Skin Cream; *Malaysia*: Ego Skin Cream; *NZ*: Ego Skin Cream; *Philipp.*: Dermalin†; Sebo Fluid†; *Singapore*: Ego Skin Cream.

Cetyl Esters

Cetylated Fatty Acids.
UNII — D072FFP9GU.

Cetyl Esters Wax

Cera Cetyla; Cera de ésteres cetílicos; Cera de ésteres del alcohol cetílico; Esperma de ballena sintético; Spermaceti Wax; Replacement; Synthetic Spermaceti; Воск Сложных Цетиловых Эфиров.
CAS — 85566-24-1.

Pharmacopoeias. In *Int.* Also in *USNF.*

USNF 31: (Cetyl Esters Wax). A mixture consisting primarily of esters of saturated fatty alcohols (C_{14} to C_{18}) and saturated fatty acids (C_{14} to C_{18}). White to off-white somewhat translucent flakes with a crystalline structure and a pearly lustre when caked; it has a faint odour and is free from rancidity. M.p. 43 degrees to 47 degrees. Insoluble in water; practically insoluble in cold alcohol; soluble in boiling alcohol, in chloroform, in ether, and in fixed and volatile oils; slightly soluble in cold petroleum spirit. Store in a dry place at a temperature not exceeding 40 degrees.

Cetyl Palmitate

Cetilo palmitatas; Cetil-palmitát; Cetyl Cetylate; Cetyle, palmitate de; Cetylis Palmitas; Cetylpalmitat; Cetyl-palmitát; Hexadecyl Palmitate; Setyylipalmitaatti; Цетилпальмитат.
Hexadecyl hexadecanoate.
$C_{32}H_{64}O_2$=480.9
CAS — 540-10-3.
UNII — 5ZA256B08X.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Cetyl Palmitate). A mixture of C_{14} to C_{18} esters of lauric (dodecanoic), myristic (tetradecanoic), palmitic (hexadecanoic) and stearic (octadecanoic) acids ('cetyl esters wax'). It contains (expressed as hexadecyl hexadecanoate): 10 to 20% for Cetyl Palmitate 15, 60 to 70% for Cetyl Palmitate 65, and not less than 90% for Cetyl Palmitate 95. White or almost white, waxy plates, flakes or powder. Practically insoluble in water and in anhydrous alcohol; soluble in boiling anhydrous alcohol and in dichloromethane; slightly soluble in light petroleum. M.p. about 45 degrees for Cetyl Palmitate 15 and Cetyl Palmitate 65, and about 52 degrees for Cetyl Palmitate 95. Store at a temperature not exceeding 25 degrees.

USNF 31: (Cetyl Palmitate). It consists of esters of cetyl alcohol and saturated high molecular weight fatty acids, principally palmitic acid. White crystals or flakes. Practically insoluble in water; freely soluble in alcohol and in ether. M.p. 46 degrees to 53 degrees. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees; avoid exposure to excessive heat above 40 degrees.

Profile

Mixtures of cetyl esters such as cetyl palmitate or cetyl esters wax are used as emollients and stiffening agents in creams and ointments. Cetyl esters wax is also used in the coating of some oral dosage forms. It is a synthetic replacement for natural spermaceti, a waxy substance obtained from the sperm whale and the bottle-nosed whale that is composed mainly of cetyl palmitate and has been used similarly.

Mixtures of cetyl esters containing mainly cetyl myristoleate have been used as nutritional supplements (see p. 2473.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Zoodermina Crema; *Fr.*: Cold Cream Naturel; *Thai.*: Hemorhin†.

Pharmacopoeial Preparations
USP 36: Rose Water Ointment.

Chlorophyll

Bladgroen; Chlorofilas; Chlorofile; Chlorofyl; Chlorophylle; Chlorophyllum; CI Natural Green 3; Cloraifili; Cloroffyl; Clorofilă; Clorofila; Clorofilla; Colour Index No. 75810; E140 (chlorophylls or chlorophyllins); Hlorofil; Hlorofils; Klorofil; Klorofill; Klorofüll; Klorofyl; Klorofyll; Lehtivihreä; Хлорофил; Хлорофилл.
CAS — 479-61-8 (chlorophyll a); 519-62-0 (chlorophyll b).

Chlorophyllin Copper Complex Sodium

Clorofilina cúprica, complejo sódico de; Медного Комплекса Хлорофиллина Натриевая Соль.

Pharmacopoeias. In *US.*

USP 36: (Chlorophyllin Copper Complex Sodium). It contains sodium salts of copper-chelated chlorophyll derivatives, but no artificial colouring. Store in airtight containers. Protect from light.

Profile

Chlorophyll is a green photosynthetic pigment found in plants, algae, and cyanobacteria (blue-green algae).

There are four closely related forms of chlorophyll. Chlorophyll a ($C_{55}H_{72}MgN_4O_5 = 893.5$) and chlorophyll b ($C_{55}H_{70}MgN_4O_6 = 907.5$) are found in plants and some types of algae; chlorophyll c, further subdivided into chlorophyll c1 ($C_{35}H_{30}MgN_4O_5 = 611.0$) and chlorophyll c2 ($C_{35}H_{28}MgN_4O_5 = 608.9$), is found in some types of algae; and chlorophyll d ($C_{54}H_{70}MgN_4O_6 = 895.5$) is found in some types of algae and in cyanobacteria.

Oil-soluble chlorophyll derivatives. Replacement of the magnesium atom in the chlorophylls by 2 hydrogen atoms using dilute mineral acids produces olive-green water-insoluble phaeophytins. Copper phaeophytins (sometimes called copper chlorophyll complex; E141) can be formed; these are more stable to acids and to light than the chlorophylls.

Water-soluble chlorophyll derivatives. When the chlorophylls are hydrolysed with alkali, phytyl alcohol and methyl alcohol are split off and green water-soluble chlorophyllins are formed as the potassium or sodium salts. Similar water-soluble compounds can be prepared in which the magnesium is replaced by copper to give copper chlorophyllin complex (E141).

Chlorophylls and chlorophyllins, as well as the copper complexes of these compounds, are used mainly as colouring agents, in foods, medicines, and cosmetics.

Chlorophyll is used clinically, as an external application in the treatment of wounds and ulcers, and as a mouthwash. There is no clear evidence that it accelerates healing but it is considered to have a deodorant action. Chlorophyllin and copper chlorophyllin complex are used similarly. Chlorophyll is also used as a dietary supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ganxuebao (肝血宝); *Ger.*: Stozzon; *Ukr.*: Chlorophyllipt (Хлорофиллипт); *USA*: Chloresium†; Derifil; Ennds; Nullo; Pals.

Multi-ingredient Preparations. *Arg.*: Panaletas; Gineseptina; Minamint; Notoxin; *Braz.*: Anapyon; Emoform Clorofila; *China*: Qianbao (乾宝); *Hong Kong*: Epilon; *Indon.*: Methaphyllin†; *Spain*: Vitavox†; *UK*: Chlorophyll; *USA*: AllanEnzyme†; AllanfillEnzyme†; Fresh-N-Free; Gladase-C†; Iron Complex; Panafil†; Papfyl; Prophyllin; Wound Cleanser; Zlox†.

Cholesterol

Cholesterin; Cholestérol; Cholesterolis; Cholesterolum; Colesterina; Colesterol; Colesterolo; Holesterins; Holesterol; Kolesterol; Kolesteroli; Kolesterool; Koleszterin; Xonecrepon; Холестерин.

Cholest-5-en-3β-ol.

$C_{27}H_{46}O = 386.7$

CAS — 57-88-5.

UNII — 97C5T2UQ7J.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Eur. also includes a form for parenteral use.

Ph. Eur. 8: (Cholesterol). A white or almost white, crystalline powder. It is sensitive to light. M.p. 147 degrees to 150 degrees. Practically insoluble in water; sparingly soluble in alcohol and in acetone. Protect from light.

Ph. Eur. 8: (Cholesterol for Parenteral Use). A white or almost white, crystalline powder. It is sensitive to light. M.p. 147 degrees to 150 degrees. Practically insoluble in water; sparingly soluble in alcohol and in acetone. Protect from light.

USNF 31: (Cholesterol). White or faintly yellow, practically odourless, pearly leaflets, needles, powder, or granules. It acquires a yellow to pale tan colour on prolonged exposure to light. M.p. 147 degrees to 150 degrees. Insoluble in water; slowly soluble 1 in 100 of alcohol; soluble 1 in 50 of dehydrated alcohol; soluble in acetone, in chloroform, in dioxan, in ether, in ethyl acetate, in petroleum spirit, and in vegetable oils. Protect from light.

Profile

Cholesterol imparts water-absorbing power to pharmaceutical preparations and is used as an emulsifying agent. It has emollient activity and is used mainly in topical preparations. It is also used in ophthalmic and vaginal formulations, and in liposomal preparations for parenteral use.

Cholesteryl benzoate (cholesterol benzoate, below) has been used as an ingredient in dermatological preparations.

Physiologically, cholesterol is an important component of cell membranes and lipoproteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Liposomas; *Chile*: Perfungol†; *Fr.*: Totephan†; *Singapore*: Ceradan.

Homoeopathic Preparations. *Canad.*: Carduus Plex†; Formula Homeo QR 209†; Hepar Compositum; *Fr.*: Bilinum Complexe No 113; Cholesterolum Complexe No 112†; Strontium Compose; *Ger.*: Chol-Do; Chole-cyl L Ho-Len-Complex; NeyArthrosome (Revitorgan-Dilution)†.

Cholesteryl Benzoate

Cholesterol Benzoate.

Cholest-5-en-3β-yl benzoate.

$C_{34}H_{50}O_2 = 490.8$

CAS — 604-32-0.

UNII — N09H13SHLB.

Profile

Cholesteryl benzoate is an ingredient in dermatological preparations; it acts as a humectant and emulsifier.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Senophile; *Fr.*: Senophile.

CI Solvent Yellow 18

CI Food Yellow 12; Colour Index No. 12740.

4-[(2,4-Dimethylphenyl)azo]-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one.

$C_{18}H_{18}N_4O = 306.4$

CAS — 6407-78-9.

Profile

CI Solvent Yellow 18 is a synthetic azo dye used as a colouring agent in contact lenses.

CI Vat Orange 1

CI Кубовый Оранжевый 1; Colour Index No. 59105.

Dibromodibenzo[b,def]chrysene-7,14-dione.

$C_{24}H_{10}Br_2O_2 = 490.2$

CAS — 1324-11-4.

Profile

CI Vat Orange 1 is a synthetic dye used as a colouring agent in contact lenses.

Citranaxanthin

Citranaksantinas; Citranaxanthine; Citranaxantina; Cytranaksantyna; E161(l); Цитранаксантин.

6′-Methyl-6′-apo-β-caroten-6′-one.

$C_{33}H_{44}O = 456.7$

CAS — 3604-90-8.

Profile

Citranaxanthin is a carotenoid pigment. It occurs naturally but is usually made synthetically and is used as a colouring agent in animal feeds, to colour the fat of poultry and the egg-yolks of laying hens. It has vitamin A activity.

Citrus Red 2

CI Solvent Red 80; Colour Index No. 12156; Цитрусовый Красный 2.

1-(2,5-Dimethoxyphenylazo)-2-naphthol.

$C_{18}H_{16}N_2O_3 = 308.3$

CAS — 6358-53-8.

UNII — 2QE5Y68984.

Profile

Citrus Red 2 is a synthetic azo dye used as a colouring agent in foods.

Cochineal

Biborteru; CI Natural Red 4; Cocciniglia del Carminio; Coccionella; Coccus; Coccus Cacti; Cochenille; Cochenilleluis; Cochenillelus; Cochinilla; Cochonilha; Colour Index No. 75470; Czerwiec kaktusowy; E120; Kokenillikirva; Koschenille; Koszenila; Кошениль.

CAS — 1343-78-8.

UNII — TZ8Z3TB35M.

Pharmacopoeias. In *Br.*

BP 2014: (Cochineal). The dried female insect, *Dactylopius coccus* containing eggs and larvae. It has a characteristic odour. It complies with a test for contamination with *Escherichia coli* and salmonellae.

Profile

Cochineal, which is a source of carmine, is used as a red colouring agent in food, medicines, and cosmetics.

There have been reports of sensitivity reactions including anaphylaxis, after use of products containing cochineal (see Hypersensitivity under Adverse Effects of Carmine, p. 2176.2).

Homoeopathy

Cochineal has been used in homoeopathic medicines under the following names: Coccus; Coccus cacti; Dactylopius coccus; Coc. c.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Port.*: Stodal.

Homoeopathic Preparations. *Austria*: Pertudoron†; *Canad.*: Drosera Complex; Drosera Plex†; Kids Cough & Cold Phytux; Male +; Pertudoron 1†; Phytotux H; Renelix; Stodal; *Cz.*: Drosetux; Stodal; *Fr.*: Baudry; Boripharm No 11†; Drosera Complexe No 64; Drosera Compose; Drosetux; L 8; Pertudoron; Stodal; Stodal; Uva Ursi Complexe No 9; *Ger.*: Bomapect N; Monapax; Pertudoron 1; Roth's RKT Tropfen; *Hung.*: Drosetux; Stodal; *Neth.*: Drosinula; Stodal; *Rus.*: Stodal (Стодаль); *S.Afr.*: Pertudoron Drops†; *Switz.*: Drosetux; Stodal; *Ukr.*: Stodal (Стодаль).

Coconut Oil

Coco (huile de) raffinee; Aceite de Coco; Cocois Oleum Raffinatum; Coconut Butter; Copra Oil; Finomitott kókuszolaj; Hindistancevizi Yağı; Klappertolie; Kokosų aliejus, rafinuotas; Kokosfett; Kokosnussöl; Kokosöl; Kokosolie; Kokosolja, raffinerad; Kokosolje; Kokosový olej, čištěný; Kokosvet; Kookosõlly, puhdistettu; Masło Kokosowe; Minyak Kelapa; Olej Kokosowy; Óleo de Coco; Oleum Cocois; Oleum Cocos Raffinatum; Oleum Cocosis; Olio di cocco; Tłuszcz Kokosowy; Кокосово Масло; Кокосовое Масло.

CAS — 8001-31-8.

UNII — O9L0O73W7L.

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

USNF includes hydrogenated coconut oil.

Ph. Eur. 8: (Coconut Oil, Refined). The refined fatty oil obtained from the dried, solid part of the endosperm of *Cocos nucifera*. A white or almost white, unctuous mass. M.p. 23 degrees to 26 degrees. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in petroleum spirit (b.p. 65 degrees to 70 degrees). Store in well-filled containers. Protect from light.

USNF 31: (Coconut oil). The refined fixed oil obtained from the seeds of *Cocos nucifera*. A clear, white to light yellow-tan, viscous liquid. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in light petroleum. M.p. 23 degrees to 26 degrees. Store in airtight, well-filled containers. Protect from light.

USNF 31: (Hydrogenated Coconut Oil). Obtained by refining and hydrogenating the oil obtained from the seeds of *Cocos nucifera*. A white to yellowish, fatty solid to semi-solid. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in ether. Store in airtight containers at a temperature not exceeding 55 degrees. Protect from light.

Uses

Coconut oil contains a mixture of mainly saturated C_6 to C_{20} fatty acids, with lauric acid and myristic acid being the most abundant. It is used as a basis for topical creams and ointments, in rectal and vaginal suppositories, in solid dosage forms, and as a plasticiser. Hydrogenated coconut oil is used similarly; it contains an even higher proportion of saturated fatty acids and melts at a higher temperature. Coconut oil is also used in food manufacturing, including infant formulas, food for special diets, and parenteral nutrition. Topical preparations have been used for pediculosis.

Fractionated coconut oil (thin vegetable oil) is used as a source of medium-chain triglycerides (p. 2082.2).

Adverse Effects

Hypersensitivity. Sensitivity reactions to coconut products, including coconut oil,[1] have been reported rarely. Cases of anaphylaxis have been reported.[2,3]

1. Couturier P, *et al.* Un cas d'allergie à l'huile de noix de coco chez un nourrisson: responsabilité des laits maternisés. *Allerg Immunol (Paris)* 1994; 26: 386–7.
2. Rosado A, *et al.* Anaphylaxis to coconut. *Allergy* 2002; 57: 182–3.
3. Nguyen SA, *et al.* Cross-reactivity between coconut and hazelnut proteins in a patient with coconut anaphylaxis. *Ann Allergy Asthma Immunol* 2004; 92: 281–4.

The symbol † denotes a preparation no longer actively marketed

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Maternity Sapolan Bronceador; *Ger.*: Aesculo Gel L; *UK*: Nitiotion.

Multi-ingredient Preparations. *Arg.*: Paranix; *Ger.*: Paranix; *India*: N-Rich Baby; *Indon.*: Minyak Telon Cap Tiga Anak†; Minyak Telon†; Telon 3 Anak; Yanthi Baby Oil†; *NZ*: Mr Nits; *Philipp.*: Enfacare; *Singapore*: Bio-Taches†; *Switz.*: Paranix; *Turk.*: Kataljin.

Cottonseed Oil

Algodón, Aceite de; Baumwollsaatöl; Baumwollsamenöl; Bomullsfröolja; Coton, huile de; Cotton Oil; Cottonöl; Gossypii Oleum; Gyapotmagolaj; Ol. Gossyp. Sem.; Oléo de Algodoeiro; Oleum Gossypii Seminis; Oli de llavors de cotó; Puuvillansiemenöljy; Vilnamedžių aliejus; Хлопковое Масло.
CAS — 8001-29-4.
UNII — H3E878020N (cottonseed oil); Z82Y2C65EA (hydrogenated cottonseed oil).

Pharmacopoeias. In *USNF*, which also includes hydrogenated cottonseed oil.

Eur. (see p. vii) includes only the hydrogenated oil.

Ph. Eur. 8: (Cottonseed Oil, Hydrogenated; Gossypii Oleum Hydrogenatum). Obtained by refining and hydrogenation of oil obtained from seeds of cultivated plants of various varieties of *Gossypium hirsutum* or of other species of *Gossypium*. It consists mainly of triglycerides of palmitic and stearic acids. It is a white or almost white mass or powder which melts to a clear pale yellow liquid when heated. M.p. 57 degrees to 70 degrees. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in toluene. Protect from light.

USNF 31: (Cottonseed Oil). The refined fixed oil obtained from the seed of plants of various varieties of *Gossypium hirsutum* or of other species of *Gossypium* (Malvaceae). It may contain suitable antoxidants. It is a pale yellow, oily liquid, odourless or nearly so. Slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, with ether, and with petroleum spirit. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light. At temperatures below 10 degrees particles of solid fat may separate from the oil and at about 0 degrees to -5 degrees the oil becomes a solid or nearly so.

USNF 31: (Hydrogenated Cottonseed Oil). It is obtained by hydrogenating Cottonseed Oil and consists mainly of triglycerides of palmitic and stearic acids. A white mass or powder that melts to a clear, pale yellow liquid when heated. M.p. 57 degrees to 70 degrees. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in toluene. Store in airtight containers. Protect from light.

Profile

Cottonseed oil is used as an oily vehicle.

An extract of cottonseed oil, gossypol (p. 2521.2), has been tried as a contraceptive in males.

Creatinine

Creatinină; Creatinina; Créatinine; Kreatiniini; Kreatinin; Kreatynina; Креатинин.
2-Amino-1-methyl-4-imidazolidinone.
$C_4H_7N_3O$=113.1
CAS — 60-27-5.
UNII — AYI8EX34EU.

Pharmacopoeias. In *Ger.* Also in *USNF*.

USNF 31: (Creatinine). White, odourless, crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone, in chloroform, and in ether.

Profile

Creatinine is used as a bulking agent for freeze-drying.

Plasma concentrations or clearance of endogenous creatinine are used as an index of renal function.

Curcumin

Colour Index No. 75300; Curcumina; Curcumine; E100; Kurkum; Kurkumin; Kurkumina; Kurkuminas; Turmeric Yellow; Куркумин.
1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione.
$C_{21}H_{20}O_6$=368.4
CAS — 458-37-7.
UNII — IT942ZTH98.

Profile

Curcumin is the main colouring component of turmeric (p. 2218.1). It is used as a colouring agent for medicines, foodstuffs, and cosmetics. Curcumin and related curcuminoids (p. 2489.3) are also used as dietary supplements. Like turmeric, they have been tried in various disorders, as they are thought to be responsible for its pharmacological activity (see p. 2218.2 for further details).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Indon.*: Curmunos; Curviplex; Dhavit; Letrosil; *Ital.*: Depatox; *UK*: Potenzia; *USA*: Immunicare; NicAzel Forte.

Cyclamic Acid *(BAN, USAN)*

Ciclámico, ácido; Cyclam. Acid; E952; Hexamic Acid; Цикламовая Кислота.
N-Cyclohexylsulphamic acid.
$C_6H_{13}NO_3S$=179.2
CAS — 100-88-9.
UNII — HN3OFO5036.

Calcium Cyclamate

Calc. Cyclam.; Calcium Cyclohexanesulfamate; Ciclamato de calcio; Ciclohexanosulfamato de calcio; Cyclamate Calcium; E952; Кальция Цикламат.
Calcium *N*-cyclohexylsulphamate dihydrate.
$C_{12}H_{24}CaN_2O_6S_2.2H_2O$=432.6
CAS — 139-06-0 (anhydrous calcium cyclamate); 5897-16-5 (calcium cyclamate dihydrate).
UNII — OK71859Z12 (calcium cyclamate); X12LMJ1WYL (anhydrous calcium cyclamate).

Potassium Cyclamate

Cyclamate Potassium; HSDB 1239; Monopotassium Cyclohexanesulfamate; Potassium Cyclohexanesulfamate; Калия Цикламат.
Potassium *N*-cyclohexysulphamate.
$C_6H_{12}NO_3SK$=217.3
CAS — 7758-04-5.
UNII — 0DS7R9NQ80.

Sodium Cyclamate *(BAN, rINN)*

Ciclamato de sodio; Ciclohexanosulfamato de sodio; Cyclamate de Sodium; Cyclamate Sodium; E952; Natrii Cyclamas; Natrio ciklamatas; Nátrium-ciklamát; Natriumcyclamat; Natriumcyklamat; Natrium-cyklamát; Natriumsykłamaatti; Siklamat Sodyum; Sod. Cyclam.; Sodium, cyclamate de; Sodium Cyclohexanesulphamate; Натрия Цикламат.
Sodium *N*-cyclohexylsulphamate.
$C_6H_{12}NNaO_3S$=201.2
CAS — 139-05-9.
UNII — 116F42RME1.

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

Ph. Eur. 8: (Sodium Cyclamate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 10% solution in water has a pH of 5.5 to 7.5.

Profile

Cyclamic acid and its salts are intense sweetening agents. In dilute solutions (up to about 0.17%) sodium cyclamate is about 30 times as sweet as sucrose but this factor decreases at higher concentrations. When the concentration approaches 0.5%, a bitter taste becomes noticeable. It is stable to heat.

The use of cyclamates as artificial sweeteners in food, soft drinks, and artificial sweetening tablets was at one time prohibited in Great Britain and some other countries because of concern about the metabolite cyclohexylamine. However, after reappraisal their use is now allowed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Sucaryl†.

Multi-ingredient Preparations. *Arg.*: Chuker; Chuker; Dulsiluet; Kaldil Diet; Rondo; Sucaryl; Suimel; *Austral.*: Sucaryl; *Braz.*: Finn Cristal; *Chile*: Endulzante; Sukar-Sin; *Fr.*: Sucaryl; *Israel*: Sucrin; *Ital.*: Diet Sucaryl†; *NZ*: Sucaryl; *Rus.*: Zuckli (Цюкли)†; *Turk.*: Dolce†; Dulcaryl; Tadalin.

Cyclodextrins

Ciclodextrinas; Циклодекстрины.

Alfadex *(BAN, rINN)*

Alfadeksas; Alfadeksi; Alfadexum; Alpha Cyclodextrin; Alphacyclodextrin; α-Cyclodextrin; Cyclohexaamylose; Cyclomaltohexose; Альфадекс.
Cyclomaltohexaose.
$C_{36}H_{60}O_{30}$=972.8
CAS — 10016-20-3.
UNII — Z1LH97KTRM.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Alfadex). A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol; practically insoluble in dehydrated alcohol and in dichloromethane. Store in airtight containers.

USNF 31: (Alfadex). A white or almost white, amorphous or crystalline, powder. Freely soluble in water and in propylene glycol; practically insoluble in dehydrated alcohol and in dichloromethane. Store in airtight containers.

Betadex *(BAN, USAN, rINN)*

Beetadeksi; Betadeksas; Bétadex; Betadexum; β-Cyclodextrin; Cycloheptaamylose; E459; Бетадекс.
Cyclo-α-(1→4)-D-heptaglucopyranoside.
$C_{42}H_{70}O_{35}$=1135
CAS — 7585-39-9.
UNII — JV039JZZ3A.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Betadex). A white or almost white, amorphous or crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in dichloromethane; freely soluble in propylene glycol. Store in airtight containers.

USNF 31: (Betadex). A nonreducing cyclic compound composed of 7 α-(1→4) linked D-glucopyranosyl units. It is a white, practically odourless, fine crystalline powder. Soluble 1 in 54 of water. Store in airtight containers.

Gamma Cyclodextrin

Cyclomaltooctaose; Cyclooctaamylose.
$C_{48}H_{80}O_{40}$=1297.1
CAS — 17465-86-0.
UNII — KZJ08YZ5VA.

Pharmacopoeias. In *USNF*.

USNF 31: (Gamma Cyclodextrin). A cyclic compound composed of 8 α-(1→4) linked D-glycopyranosyl units. A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol; very slightly soluble in alcohol.

Hydroxypropylbetadex

Hidroksipropilbetadeksas; Hydoxipropylbetadex; Hydroksipropyylibetadeksi; Hydroxypropylbétadex; Hydroxypropylbetadexum; 2-Hydroxypropyl-β-cyclodextrin.
UNII — 1196OHX6EK (hydroxypropylbetadex (0.58-0.68 ms)).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Hydroxypropylbetadex). A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol.

USNF 31: (Hydroxypropyl Betadex). A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol.

Profile

Cyclodextrins, such as alfadex, betadex, and gamma cyclodextrin, are cyclic oligosaccharides obtained by enzymatic degradation of starch. They form inclusion compounds with a wide range of molecules and are used as carriers for oral, parenteral, and topical drug delivery systems. They improve dissolution and solubility, increase stability, and may also be used for taste-masking. Substituted cyclodextrins such as hydroxypropylbetadex, sulfobutylether-β-cyclodextrin, and dimethyl-β-cyclodextrin are also used.

Cyclodextrins are also used in the food industry.

References.
1. Stella VJ, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. *Pharm Res* 1997; 14: 556–67.
2. Loftsson T, Olafsson JH. Cyclodextrins: new drug delivery systems in dermatology. *Int J Dermatol* 1998; 37: 241–6.
3. Redenti E, *et al.* Drug/cyclodextrin/hydroxy acid multicomponent systems: properties and pharmaceutical applications. *J Pharm Sci* 2000; 89: 1–8.

4. Loftsson T, Masson M. Cyclodextrins in topical drug formulations: theory and practice. *Int J Pharm* 2001; **225:** 15–30.
5. Loftsson T, Stefansson E. Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye. *Acta Ophthalmol Scand* 2002; **80:** 144–50.
6. Dass CR. Cyclodextrins and oligonucleotide delivery to solid tumours. *J Drug Target* 2004; **12:** 1–9.
7. Kaur IP, *et al.* Role of cyclodextrins in ophthalmics. *Curr Drug Deliv* 2004; **1:** 351–60.
8. Challa R, *et al.* Cyclodextrins in drug delivery: an updated review. *AAPS PharmSciTech* 2005; **6:** E329–E357.
9. Loftsson T, Duchêne D. Cyclodextrins and their pharmaceutical applications. *Int J Pharm* 2007; **329:** 1–11.
10. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. *Adv Drug Deliv Rev* 2007; **59:** 645–66.
11. Carrier RL, *et al.* The utility of cyclodextrins for enhancing oral bioavailability. *J Control Release* 2007; **123:** 78–99.
12. Cal K, Centkowska K. Use of cyclodextrins in topical formulations: practical aspects. *Eur J Pharm Biopharm* 2008; **68:** 467–78.
13. Stella VJ, He Q. Cyclodextrins. *Toxicol Pathol* 2008; **36:** 30–42.
14. Otero-Espinar FJ, *et al.* Cyclodextrins: more than pharmaceutical excipients. *Mini Rev Med Chem* 2010; **10:** 715–25.

Cyclohexane

Cicloexano; Ciclohexa; Ciclohexano; Cikloheхán; Cyclohexaan; Cyclohexan; Cyclohexano; Cykloheksan; Cyklohexan; Hexahidroxibenzeno; Hexahydrobenzene; Hexamethylene; Hexametileno; Hexanafteno; Sykloheksaani; Sykloheksan; Циклогексан; Циклохексан.

C_6H_{12}=84.16

CAS — 110-82-7.

UNII — 48K5MKG32S.

Description. Cyclohexane is a colourless, flammable liquid. Wt per mL about 0.78 g. B.p. about 81 degrees. Store in airtight containers.

Uses

Cyclohexane is used as an industrial solvent.

Adverse Effects

Cyclohexane is irritant, and may also have effects on the CNS.

Reviews of the toxicity of cyclohexane.

1. Health and Safety Executive. Cyclohexane, cumene, para-dichlorobenzene (p-DCB), chlorodifluoromethane (CPC 22). *Toxicity Review 25.* London: HMSO, 1991.

Denatonium Benzoate *(BAN, USAN, rINN)*

Benzoate de dénatonium; Benzoato de denatonio; Benzoesan denatonium; Denatonii Benzoas; Denatonio, benzoato de; Dénatonium, Benzoate de; Denatoniumbensoat; Denatonium-Bentsoaatti; Denatoniumbenzoaat; Denatoniumbenzoat; Denatoniumbenzoát; NSC-157658; Денатония Бензоат.

Benzyldiethyl(2,6-xylylcarbamoylmethyl)ammonium benzoate monohydrate.

$C_{28}H_{34}N_2O_3,H_2O$=464.6

CAS — 3734-33-6 (anhydrous denatonium benzoate); 86398-53-0 (denatonium benzoate monohydrate).

UNII — 4YK5Z54AT2.

Pharmacopoeias. In *USNF.*

USNF 31: (Denatonium Benzoate). When dried at 105 degrees for 2 hours, it contains one molecule of water of hydration or is anhydrous. Soluble 1 in 20 of water, 1 in 2.4 of alcohol, 1 in 2.9 of chloroform, and 1 in 5000 of ether; very soluble in methyl alcohol. pH of a 3% solution in water is between 6.5 and 7.5. Store in airtight containers.

Profile

Denatonium benzoate is used where an intensely bitter taste is required for medicinal or industrial purposes and as a partial denaturant for alcohol in toiletries. It is known commercially as Bitrex.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.:* Skin Nail.

Dextrates *(USAN)*

Dextratos.

CAS — 39404-33-6.

UNII — G263MI44RU.

Pharmacopoeias. In *USNF.*

USNF 31: (Dextrates). A purified, anhydrous or hydrated, mixture of saccharides obtained by the controlled enzymatic hydrolysis of starch. Free-flowing, porous, white, odourless, spherical granules consisting of aggregates of microcrystals. Freely soluble in water (heating increases its solubility in water); soluble in dilute acids and alkalis and in basic organic solvents such as pyridine; insoluble in the common organic solvents. pH of a 20% solution in water is between 3.8 and 5.8. Store in a dry place at a temperature of 8 degrees to 15 degrees.

Profile

Dextrates are used as a capsule and tablet diluent and as a tablet binding agent.

Dibutyl Sebacate

Dibutylsebacaat; Sebacato de dibutilo; Sebacinsäuredibutylester; Дибутилсебацинат.

Dibutyl decanedioate.

$C_{18}H_{34}O_4$=314.5

CAS — 109-43-3.

UNII — 4W5IH7FLNY.

Pharmacopoeias. In *USNF.*

USNF 31: (Dibutyl Sebacate). It consists of esters of *n*-butyl alcohol and saturated dibasic acids, principally sebacic acid. A colourless, oily liquid of very mild odour. Practically insoluble in water and in glycerol; soluble in alcohol, in isopropyl alcohol, and in liquid paraffin; very slightly soluble in propylene glycol. Store in airtight containers. Protect from moisture.

Profile

Dibutyl sebacate is a plasticiser used in pharmaceutical formulation of tablets (including modified release), beads, and granules, and microcapsule preparations. It is also used as a food flavouring.

Dichloromethane

Cloruro de metileno; Dichloormethaan; Dichlormethan; Diclorometano; Dikloorimetaani; Diklormetan; Diklórmetán; Methylene Chloride; Méthylène, chlorure de; Methyleni Chloridum; Metilénhloridas; Metileno chloridas; Metüleenkloriid; Metyleenikloridi; Metylenklorid; Metylenu chlorek; Дихлорметан.

CH_2Cl_2=84.93

CAS — 75-09-2.

UNII — 588X2YUY0A.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Methylene Chloride; Dichloromethane BP 2014). A clear, colourless, volatile liquid. Relative density 1.320 to 1.332. It may contain not more than 2% of alcohol and/or not more than 0.03% of 2-methylbut-2-ene as stabiliser. Sparingly soluble in water; miscible with alcohol. Store in airtight containers. Protect from light.

USNF 31: (Methylene Chloride). A clear, colourless, mobile liquid having an odour resembling chloroform. Sp. gr. 1.318 to 1.322. Miscible with alcohol, with ether, and with fixed and volatile oils. Store in airtight containers.

Stability. Phosgene is produced on heating of dichloromethane.

Uses

Dichloromethane is used as a pharmaceutical and industrial solvent, and as an extraction solvent in food processing.

Dichloromethane is widely used in paint strippers.

Adverse Effects and Treatment

Acute exposure to dichloromethane vapour may depress the CNS; symptoms progress from headache and dizziness to coma and death in severe cases. Pulmonary oedema has been reported. Significant exposure may result in raised blood concentrations of carboxyhaemoglobin and symptoms of carbon monoxide poisoning. Cardiovascular effects have been attributed to hypoxia secondary to carboxyhaemoglobinaemia. There has been a report of haemolysis after acute ingestion of dichloromethane.

Chronic occupational exposure to dichloromethane vapour has produced gastrointestinal disturbances in addition to symptoms seen after acute poisoning. Dichloromethane is a common constituent of paint strippers and may be implicated in volatile substance abuse (see under Toluene, p. 2216.3).

The liquid is irritant and high concentrations of the vapour are irritant to the eyes.

Treatment of acute poisoning consists of removal from exposure and supportive and symptomatic measures. Carboxyhaemoglobinaemia should be managed as for carbon monoxide poisoning (p. 1798.1) by giving 100% oxygen. After ingestion gastric lavage or activated charcoal are generally contra-indicated.

References.

1. WHO. Methylene Chloride. *Environmental Health Criteria 32.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc32.htm (accessed 29/06/04)
2. Health and Safety Executive. Dichloromethane (methylene chloride). *Toxicity Review 12.* London: HMSO,1985.
3. WHO. Methylene chloride health and safety guide. *IPCS Health and Safety Guide 6.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg006.htm (accessed 29/06/04)
4. Rioux JP, Myers RAM. Methylene chloride poisoning: a paradigmatic review. *J Emerg Med* 1988; **6:** 227–38.
5. Manno M, *et al.* Double fatal inhalation of dichloromethane. *Hum Exp Toxicol* 1992; **11:** 540–5.
6. Dhillon S, Von Burg R. Methylene chloride. *J Appl Toxicol* 1995; **15:** 329–35.
7. IARC/WHO. Dichloromethane. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 251–315. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)
8. Chang YL, *et al.* Diverse manifestations of oral methylene chloride poisoning: report of 6 cases. *J Toxicol Clin Toxicol* 1999; **37:** 497–504.
9. Jacubovich RM, *et al.* Facial nerve palsy after acute exposure to dichloromethane. *Am J Ind Med* 2005; **48:** 389–92.

Pharmacokinetics

Dichloromethane is rapidly absorbed after inhalation and is also absorbed after ingestion and slowly through intact skin. It appears to be partially metabolised to carbon dioxide and carbon monoxide which are exhaled, although significant blood-carboxyhaemoglobin concentrations may be attained. Some unchanged dichloromethane is exhaled and small amounts are excreted in the urine.

Dichloropropane

Dicloropropano; Dicloruro de propileno; Propylene Dichloride; Дихлорпропан.

1,2-Dichloropropane.

$C_3H_6Cl_2$=113.0

CAS — 78-87-5.

UNII — RRZ023OFWL.

Description. Dichloropropane is a colourless, mobile, flammable liquid. Wt per mL about 1.16 g. B.p. about 96 degrees. Store in airtight containers.

Uses

Dichloropropane is used as an industrial solvent, dry cleaning agent, and agricultural defumigant.

Adverse Effects and Treatment

Dichloropropane is an irritant to the respiratory tract, eyes, and skin. Both acute and chronic exposure to dichloropropane may cause liver and kidney damage. Ingestion causes nausea, vomiting, diarrhoea, abdominal pain, headache, CNS depression, disseminated intravascular coagulation, and haemolytic anaemia. Inhalation produces similar effects to ingestion.

Acute exposure to dichloropropane should be treated with supportive and symptomatic therapy. Activated charcoal may be given to those who present within 1 hour of ingestion.

References.

1. Locatelli F, Pozzi C. Relapsing haemolytic-uraemic syndrome after organic solvent sniffing. *Lancet* 1983; **ii:** 220.
2. IARC/WHO. 1,2-Dichloropropane. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 1393–1400. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)
3. Lazo-Torres AM, *et al.* Intoxicación por dicloropropano: comunicación de 2 casos. *Med Clin (Barc)* 2005; **124:** 318.

Diethyl Phthalate

DEP; Diéthyle, phtalate de; Diethylftalaat; Diethyl-ftalát; Diethylis Phthalas; Diethylphthalat; Dietil-ftalát; Dietilo ftalatas; Dietylftalat; Dietyyliftalaatti; Ethyl Phthalate; Ftalato de dietilo; Диэтилфталат.

Benzene-1,2-dicarboxylic acid diethyl ester.

$C_{12}H_{14}O_4$=222.2

CAS — 84-66-2.

UNII — UF064M00AF.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.* Also in *USNF.*

Ph. Eur. 8: (Diethyl Phthalate). A clear, colourless or very slightly yellow, oily liquid. Relative density 1.117 to 1.121. Practically insoluble in water; miscible with alcohol. Store in airtight containers.

USNF 31: (Diethyl Phthalate). A colourless, practically odourless, oily liquid. Sp. gr. 1.118 to 1.122 at 20 degrees. Insoluble in water; miscible with alcohol, with ether, and with other usual organic solvents. Store in airtight containers.

Uses

Diethyl phthalate is used as a denaturant of alcohol, for example in surgical spirit, and as a solvent and plasticiser.

Adverse Effects

Diethyl phthalate is irritant and, in high concentrations, causes CNS depression. There has been concern about potential toxicity resulting from exposure to phthalates used as plasticisers.

References.
1. Health and Safety Executive. Review of the toxicity of the esters of o-phthalic acid (phthalate esters). *Toxicity Review 14*. London: HMSO,1986.
2. Kamrin MA. Mayor GH. Diethyl phthalate: a perspective. *J Clin Pharmacol* 1991; 31: 484–9.
3. Shea KM, *et al.* American Academy of Pediatrics Technical Report. Pediatric exposure and potential toxicity of phthalate plasticizers. *Pediatrics* 2003; 111: 1467–74. [Re-affirmed May 2009. Retired January 2011]
4. Kamrin MA. Phthalate risks, phthalate regulation, and public health: a review. *J Toxicol Environ Health B* 2009; 12: 157–74.

Preparations

Pharmacopoeial Preparations
BP 2014: Surgical Spirit.

Diethylene Glycol Esters

Diglycol Esters; PEG-2 Esters; Polyethylene Glycol 100 Esters.

NOTE. The nomenclature used for these esters is potentially confusing. Diethylene glycol is an ethylene oxide polymer and has thus sometimes been referred to as a polyethylene glycol (*macrogol*) although this term is more usually applied to oligomers containing larger numbers of ethylene glycol units. The molecular weight of diethylene glycol is slightly over 100, and esters of diethylene glycol have therefore sometimes been termed polyethylene glycol 100 esters.

Diethylene Glycol Monolaurate

Diethylene Glycol Laurate; Diglycol Laurate; PEG-2 Laurate; Polyethylene Glycol 100 Laurate.
2-(2-Hydroxyethoxy)ethyl dodecanoate.
$C_{16}H_{32}O_4$=288.4
CAS — 141-20-8.

Diethylene Glycol Mono-oleate

Diethylene Glycol Oleate; Diglycol Oleate; PEG-2 Oleate; Polyethylene Glycol 100 Oleate.
2-(2-Hydroxyethoxy)ethyl octadecenoate.
$C_{22}H_{42}O_4$=370.6
CAS — 106-12-7.

Diethylene Glycol Monostearate

Diethylene Glycol Stearate; Diglycol Stearate; PEG-2 Stearate; Polyethylene Glycol 100 Stearate.
2-(2-Hydroxyethoxy)ethyl octadecanoate.
$C_{22}H_{44}O_4$=372.6
CAS — 106-11-6.

NOTE. The name Diethylene Glycol Stearate has also been used for the palmitostearate (below).

Diethylene Glycol Palmitostearate

Diethylene Glycol Monopalmitostearate; Diéthylèneglycol, palmitostéarate de; Diethylenglycoli Monopalmitostearas; Diethylenglycoli Palmitostearas; Diethylenglykol monopalmitostearát; Diethylenglykol palmito stearát; Dietilenglicol, monopalmitoestearato de; Dietilenglikolio palmitostearatas; Dietilénglikol-monopalmitát és monosztearát; Dietyleenieglykolipalmitostearaatti; Dietylenglykolpalmitostearat; *Диэтиленгликоля Монопальмитостеарат.*
CAS — 106-11-6 (diethylene glycol monostearate); 36381-62-1 (diethylene glycol monopalmitate); 109-30-8 (diethylene glycol distearate).
UNII — 5A70WD5W3Z (diethylene glycol palmitostearate); 94YQ11Y95F (diethylene glycol stearate).

Pharmacopoeias. In *Eur.* (see p. vii). *USNF* includes Diethylene Glycol Stearates.

Ph. Eur. 8: (Diethylene Glycol Palmitostearate). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids produced by esterification of diethylene glycol and stearic acid of vegetable or animal origin. It contains 45.0 to 60.0% of monoesters and 35.0 to 55.0% of diesters, and a maximum of 2.5% of free diethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43 degrees to 50 degrees. Protect from light.

USNF 31: (Diethylene Glycol Stearates). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 45.0% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43 degrees to 50 degrees. Store in airtight containers.

Profile

Diethylene glycol esters are esters of fatty acids with diethylene glycol. They are glycol ester nonionic surfactants (p. 2164.2) and have similar properties to glycerol esters (see under Glyceryl Palmitostearate, p. 2187.2). Diethylene glycol palmitostearate is used as an emulsifier and emollient in topical cosmetic and pharmaceutical preparations. The monolaurate and mono-oleate are used in cosmetic and personal care products.

Diethylene Glycol Ethers

PEG-2 Ethers; Polyethylene Glycol 100 Ethers; Polyoxyl 2 Ethers.

Diethylene Glycol Monoethyl Ether

Carbitol; DEGMEE; Diéthylèneglycol, éther monoéthylique de; Diethylenglycoli monoethylicum aetherum; Diethylenglycoli Monoethylicum Etherum; Diethylenglycolmonoethylether; Diethylenglykolmonoethyl ether; Dietilenglikolio monoetilo eteris; Dietilénglikol-monoetiléter; Dietyleenieglykolimonoetyylieetteri; Dietylenglykolmonoetyleter; Ethoxydiglycol.
3,6-Dioxaoctan-1-ol; 2-(2-Ethoxyethoxy)ethanol.
$C_6H_{14}O_3$=134.2
CAS — 111-90-0.
UNII — A1A1I8X02B.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Diethylene Glycol Monoethyl Ether). 2-(2-Ethoxyethoxy)ethanol, produced by condensation of ethylene oxide and alcohol, followed by distillation. A clear, colourless, hygroscopic liquid. Miscible with water, with acetone and with alcohol; miscible in certain proportions with vegetable oils; not miscible with mineral oils. Relative density about 0.991. Store in an airtight container under an inert gas.

USNF 31: (Diethylene Glycol Monoethyl Ether). Produced by condensation of ethylene oxide and alcohol, followed by distillation. A clear, colourless, hygroscopic liquid. Miscible with water, with acetone, and with alcohol; partially miscible with vegetable oils; immiscible with mineral oils. Specific gravity about 0.991. Store in airtight containers under an atmosphere of an inert gas, at a temperature not exceeding 35 degrees.

Profile

Diethylene glycol monoethyl ether is a glycol ether nonionic surfactant (p. 2164.2) used as a solubiliser and solvent. The monomethyl ether is also used.

Diethylene glycol ethers with fatty alcohols are also used but are included under the corresponding macrogol ethers.

Diisopropanolamine

Diisopropanolamina; Диизопропаноламин.
1,1′-Iminobis(propan-2-ol).
$C_6H_{15}NO_2$=133.2
CAS — 110-97-4.
UNII — 0W44HYL8TS.

Pharmacopoeias. In *USNF.*

USNF 31: (Diisopropanolamine). A mixture of isopropanolamines, consisting largely of diisopropanolamine. Store in airtight containers. Protect from light.

Profile

Diisopropanolamine is an organic base that is used as a neutralising agent in cosmetics and toiletries.

Dimethyl Sulfoxide *(BAN, USAN, rINN)*

Dimethyl Sulphoxide; Dimethyli Sulfoxidum; Dimethylis Sulfoxidum; Dimethylsulfoxid; Diméthylsulfoxyde; Dimetil Sülfoksit; Dimetil sulfóxido; Dimetilsolfossido; Dimetilsulfoksidas; Dimetilsulfóxido; Dimetil-szulfoxid; Dimetylosulfotlenek; Dimetylsulfoxid; Dimetyylisulfoksidi; DMSO; Methyl Sulphoxide; NSC-763; SQ-9453; Sulfóxido de dimetilo; Sulphinylbismethane; *Диметилсульфоксид.*
C_2H_6OS=78.13
CAS — 67-68-5.
ATC — G04BX13; M02AX03.
ATC Vet — QG04BX13; QM02AX03.
UNII — YOW8V9698H.

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

Ph. Eur. 8: (Dimethyl Sulfoxide). A colourless hygroscopic liquid or crystals. F.p. not lower than 18.3 degrees. Relative density 1.100 to 1.104. Miscible with water and with alcohol. Store in airtight glass containers. Protect from light.

USP 36: (Dimethyl Sulfoxide). A clear, colourless, odourless, hygroscopic liquid. M.p. about 18.4 degrees. Sp. gr. 1.095 to 1.097. Soluble in water; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Dimethyl sulfoxide is a highly polar substance with exceptional solvent properties for both organic and inorganic chemicals, and is widely used as an industrial solvent.

It has been reported to have a wide spectrum of pharmacological activity including membrane penetration, anti-inflammatory effects, local analgesia, weak bacteriostasis, diuresis, vasodilatation, dissolution of collagen, and free-radical scavenging.

The principal use of dimethyl sulfoxide is as a vehicle for drugs such as idoxuridine (p. 985.1); it aids penetration of the drug into the skin, and so may enhance the drug's effect. It is also used as a 50% aqueous solution for bladder instillation for the symptomatic relief of interstitial cystitis; doses of 50 mL are instilled and allowed to remain for 15 minutes. Treatment is repeated every 2 weeks initially.

Dimethyl sulfoxide has been given orally, intravenously, or topically for a wide range of indications including cutaneous and musculoskeletal disorders, but evidence of beneficial effects is limited.

Dimethyl sulfoxide is used as a cryoprotectant for various human tissues.

Amyloidosis. Oral or local dimethyl sulfoxide has been tried[1-3] as part of the management of some forms of amyloidosis (p. 819.3).

1. Ichida M, *et al.* Successful treatment of multiple myeloma-associated amyloidosis by interferon-alpha, dimethyl sulfoxide, and VAD (vincristine, adriamycin, and dexamethasone). *Int J Hematol* 2000; 72: 491–3.
2. Malek RS, *et al.* Primary localized amyloidosis of the bladder: experience with dimethyl sulfoxide therapy. *J Urol (Baltimore)* 2002; 168: 1018–20.
3. Amemori S, *et al.* Oral dimethyl sulfoxide for systemic amyloid A amyloidosis complication in chronic inflammatory disease: a retrospective patient chart review. *J Gastroenterol* 2006; 41: 444–9.

Cryopreservation. Dimethyl sulfoxide is used as a cryoprotectant in various assisted conception techniques.[1] Adverse effects have been reported in patients receiving haematopoietic stem cells cryopreserved in dimethyl sulfoxide (see under Adverse Effects, p. 2183.1).

1. Trounson AO. Cryopreservation. *Br Med Bull* 1990; 46: 695–708.

Extravasation of antineoplastics. Several reports have suggested a role for topical dimethyl sulfoxide in the treatment of anthracycline extravasation.[1-4] The problem of antineoplastic extravasation and its management is discussed further on p. 731.3.

1. Lawrence HJ, Goodnight SH. Dimethyl sulfoxide and extravasation of anthracycline agents. *Ann Intern Med* 1985; 98: 1025.
2. Olver IN, *et al.* A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. *J Clin Oncol* 1988; 6: 1732–5.
3. Rospond RM, Engel LM. Dimethyl sulfoxide for treating anthracycline extravasation. *Clin Pharm* 1993; 12: 560–1.
4. Bertelli G, *et al.* Dimethylsulphoxide and cooling after extravasation of antitumour agents. *Lancet* 1993; 341: 1098.

Interstitial cystitis. Bladder instillation of dimethyl sulfoxide is used[1,2] in the symptomatic management of interstitial cystitis (p. 2348.1). Treatment usually consists of 50 mL of a 50% aqueous solution that is retained in the bladder for 15 minutes. This may be repeated every 1 to 2 weeks for 4 to 8 treatments, and overall response rates of 50 to 90% have been reported. Although relapse rates after a 4- to 8-week course of treatment are high (35 to 40%), about half of these patients will respond to additional dimethyl sulfoxide treatment. Maintenance therapy on either a regular or intermittent basis may be used.[1]

1. Parkin J, *et al.* Intravesical dimethyl sulfoxide (DMSO) for interstitial cystitis—a practical approach. *Urology* 1997; 49 (suppl 5A): 105–7.
2. Rösberger J, *et al.* Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome. *Scand J Urol Nephrol* 2005; 39: 73–7.

Osteoarthritis. Dimethyl sulfoxide has been applied topically in the treatment of osteoarthritis (p. 12.3) but a systematic review, which noted that empirical reports had suggested concentrations of 60 to 90% dimethyl sulfoxide were needed topically for therapeutic effect, found that it was not possible to draw any conclusions as to benefit;[1] many studies used suboptimal concentrations or were over inadequate time periods.

1. Brien S, *et al.* Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthritis Cartilage* 2008; 16: 1277–88.

Adverse Effects and Treatment

High concentrations of dimethyl sulfoxide applied to the skin may cause burning discomfort, itching, erythema, vesiculation, and urticaria. Continued use may result in scaling.

Systemic effects, including gastrointestinal disturbances, drowsiness, headache, and hypersensitivity reactions, may occur after use by any route. A garlic-like odour on the breath and skin is attributed to the formation of dimethyl sulfide (see Pharmacokinetics, below). Intravascular haemolysis has followed intravenous use. Local discomfort and spasm may occur when given by bladder instillation.

Treatment of adverse effects consists of symptomatic and supportive measures.

Reviews.

1. Brobyn RD. The human toxicology of dimethyl sulfoxide. *Ann N Y Acad Sci* 1975; 243: 497–506.
2. Willhite CC, Katz FL. Toxicology updates: dimethyl sulfoxide. *J Appl Toxicol* 1984; 4: 155–60.

Dimethyl sulfoxide given by intravenous infusion for spinal cord injury to 14 patients caused transient haemolysis and haemoglobinuria.[1] Infusion strengths greater than 10% were associated with grossly discoloured urine but there was no evidence of renal damage. In 2 patients, raised liver and muscle enzyme concentrations, mild jaundice, and evidence of haemolysis developed when given dimethyl sulfoxide intravenously for arthritis.[2] One also developed acute renal tubular necrosis, deterioration in level of consciousness, and evidence of cerebral infarction. Acute, reversible neurological deterioration in a patient has been associated with intravenous dimethyl sulfoxide.[3]

Adverse effects have also been reported in patients given haematopoietic stem cells cryopreserved in dimethyl sulfoxide. A patient with pre-existing diabetes insipidus[4] developed serum hyperosmolality when given stem cells after chemotherapy for a malignant germ-cell tumour; symptoms included severe headache, confusion, and abdominal pain. Acute neurotoxicity has also been reported,[5,6] although it appears to be rare;[5] 2 patients also had myocardial damage.[6]

1. Muther RS, Bennett WM. Effects of dimethyl sulfoxide on renal function in man. *JAMA* 1980; 244: 2081–3.
2. Yellowlees P, *et al.* Dimethylsulphoxide-induced toxicity. *Lancet* 1980; ii: 1004–6.
3. Bond GR, *et al.* Dimethylsulphoxide-induced encephalopathy. *Lancet* 1989; i: 1134–5.
4. Thomé S, *et al.* Dimethylsulphoxide-induced serum hyperosmolality after cryopreserved stem-cell graft. *Lancet* 1994; 344: 1431–2.
5. Mueller LP, *et al.* Neurotoxicity upon infusion of dimethylsulfoxide-cryopreserved peripheral blood stem cells in patients with and without pre-existing cerebral disease. *Eur J Haematol* 2007; 78: 527–31.
6. Chen-Plotkin AS, *et al.* Encephalopathy, stroke, and myocardial infarction with DMSO use in stem cell transplantation. *Neurology* 2007; 68: 859–61.

Precautions

When used as a penetrating basis for other drugs applied topically, dimethyl sulfoxide may enhance their toxic effects.

Since dimethyl sulfoxide has been associated with lens changes in *animals*, licensed product information recommends assessment of ophthalmic function every 6 months during long-term treatment of cystitis with intravesical instillation of dimethyl sulfoxide. Hepatic and renal function should also be assessed at intervals of 6 months. Bladder instillation may be harmful in patients with urinary-tract malignancy because of vasodilatation.

Interactions

Increased psychomotor impairment has been reported in patients who drank alcohol after topical exposure to dimethyl sulfoxide, including inadvertent occupational exposure.

For mention of an interaction between dimethyl sulfoxide and *sulindac*, see p. 135.2.

Pharmacokinetics

Dimethyl sulfoxide is readily absorbed by all routes. It is metabolised by oxidation to dimethyl sulfone (p. 2493.3) and by reduction to dimethyl sulfide. Dimethyl sulfoxide and the sulfone metabolite are excreted in the urine and faeces. Dimethyl sulfide is excreted through the lungs and skin and is responsible for the characteristic odour from patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Kemsol†; Rimso; *Rus.*: Prostatilen (Простатилен); Silocast (Силокаст); *UK*: Rimso; *USA*: Rimso.

Multi-ingredient Preparations. *Arg.*: Verrugard; *Austria*: Dolobene; Verrumal; *Braz.*: Dolobene†; *China*: Dolobene (瑞乐平); *Cz.*: Dolobene; Verrumal; *Ger.*: Dolobene†; GeloBacin; Verrumal; *Hong Kong*: Dolobene†; Verrumal; *Hung.*: Dolobene; Verra-med; Verrumal; *Israel*: Verrumal; *Malaysia*: Verrumal; *Pol.*: Brodacid; Dolobene†; *Rus.*: Capsicam (Капсикам); Chondroitine-Akos (Хондроитин-Акос); Chondroxide (Хондроксид); Dolobene (Долобене); Espol (Эспол); Hondrofen (Хондрофен); *Singapore*: Verrumal; *Spain*: Artrodesmol Extra; *Switz.*: Assan rem; Dolo Demotherm†; Dolobene; Histalgane mite; Histalgane; Sportusal Spray sine heparino; Sportusal; Venucreme; Venugel; Verra-med; Verrumal; *Thai.*: Verrumal; *Ukr.*: Capsicam (Капсикам); Chondrasil (Хондрасил)†; Chondroxide (Хондроксид); Dolobene (Долобене); Phytobene (Фитобене).

Pharmacopoeial Preparations

USP 36: Dimethyl Sulfoxide Irrigation.

Dimethylacetamide

Acetyldimethylamine; Acido acético dimetilamida; Dimethylacetamide; Dimethylacetamid; Dimethylacetamide; Dimethylacetamidum; Dimetilacetamida; Dimetilacetamidas; Dimetilacetammide; Dimetylacetamid; Dimetyletanamid; Dimetyloacetamid; Dimetyylasetamidi; DMAC; Диметилацетамид.

NN-Dimethylacetamide.

C_4H_9NO=87.12

CAS — 127-19-5.

UNII — JCV5VD83HY.

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

Ph. Eur. 8: (Dimethylacetamide). A clear, colourless, slightly hygroscopic liquid. Relative density 0.941 to 0.944. B.p. about 165 degrees. Miscible with water, with alcohol, and with most common organic solvents. Store in airtight containers. Protect from light.

Uses

Dimethylacetamide is used as an industrial and pharmaceutical solvent.

Adverse Effects and Precautions

As for Dimethylformamide (below), although a disulfiram-like reaction with alcohol has not been reported.

A review[1] of the toxicology of dimethylacetamide with reference to its use as a vehicle for antineoplastics. A pharmacokinetic study[2] of the use of dimethylacetamide in children found no safety concerns. However, reversible hepatotoxicity has been reported[3] after occupational exposure.

1. Kim S-N. Preclinical toxicology and pharmacology of dimethylacetamide, with clinical notes. *Drug Metab Rev* 1988; 19: 345–68.
2. Hempel G, *et al.* Cytotoxicity of dimethylacetamide and pharmacokinetics in children receiving intravenous busulfan. *J Clin Oncol* 2007; 25: 1772–8.
3. Jung S-J, *et al.* Dimethylacetamide-induced hepatic injuries among spandex fibre workers. *Clin Toxicol* 2007; 45: 435–9.

Handling. Suitable precautions should be taken to avoid skin contact with dimethylacetamide as it can penetrate skin and produce systemic toxicity.

Dimethylformamide

Dimethylformamid; Dimethylformamide; Dimetilamida del ácido fórmico; Dimetilformamid; Dimetilformamida; Dimetilformammide; Dimetylformamid; Dimetyloformamid; DMF; Диметилформамид.

NN-Dimethylformamide.

C_3H_7NO=73.10

CAS — 68-12-2.

UNII — 8696NH0Y2X.

Description. Dimethylformamide is a colourless liquid. Wt per mL about 0.95 g. B.p. about 153 degrees.

Uses

Dimethylformamide is used as an industrial solvent.

Adverse Effects and Precautions

Dimethylformamide is irritant. Gastrointestinal effects including nausea, vomiting, loss of appetite, and abdominal pain, CNS effects such as headache, dizziness, and weakness, and liver damage have been reported in workers occupationally exposed to the liquid or vapour. Some workers exposed to dimethylformamide have had a disulfiram-like effect after consumption of alcohol.

Reviews of the adverse effects of dimethylformamide.

1. WHO. Dimethylformamide. *Environmental Health Criteria 114.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc114.htm (accessed 30/06/04)
2. IARC/WHO. Dimethylformamide. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; 71: 545–74. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

Effects on the liver. Exposure to dimethylformamide was considered to be the most likely cause of elevated liver enzyme values in 36 of 58 (62%) workers in a fabric coating factory.[1] Symptoms reported were generally mild and included anorexia, abdominal pain, nausea, headache, dizziness, and a disulfiram-type reaction to alcohol. In another report,[2] 3 of 4 workers with probable dimethylformamide liver toxicity presented with skin eruptions.

Hepatotoxicity has occurred after acute poisoning with a veterinary drug formulated in dimethylformamide. There were only minor increases in liver enzyme values in a patient who was treated early with acetylcysteine.[3]

1. Redlich CA, *et al.* Liver disease associated with occupational exposure to the solvent dimethylformamide. *Ann Intern Med* 1988; 108: 680–6.
2. Hamada M, *et al.* Occupational liver injury due to N,N-dimethylformamide in the synthetics industry. *Intern Med* 2009; 48: 1647–50.
3. Buylaert W, *et al.* Hepatotoxicity of N,N-dimethylformamide (DMF) in acute poisoning with the veterinary euthanasia drug T-61. *Hum Exp Toxicol* 1996; 15: 607–11.

Handling. Suitable precautions should be taken to avoid skin contact with dimethylformamide as it can penetrate skin and produce systemic toxicity.

Malignant neoplasms. There have been reports of testicular cancer in men occupationally exposed to dimethylformamide.[1] Such an association could not, however, be substantiated by epidemiological data[2] on 3859 male employees exposed to dimethylformamide between 1950 and 1970 and followed up to 1984. It has been suggested that although dimethylformamide may not itself be carcinogenic, it may increase absorption through the skin of heavy metal carcinogens, possibly including chromates.[3]

1. Levin SM, *et al.* Testicular cancer in leather tanners exposed to dimethylformamide. *Lancet* 1987; ii: 1153.
2. Chen JL, Kennedy GL. Dimethylformamide and testicular cancer. *Lancet* 1988; i: 55.
3. Ducatman AM. Dimethylformamide, metal dyes, and testicular cancer. *Lancet* 1989; i: 911.

Pharmacokinetics

Dimethylformamide is absorbed after inhalation and through intact skin. It is excreted mainly in the urine as metabolites.

Diolamine (*pINN*)

Diaethanolamin; Dietanolamina; Dietanolammina; Dietanoloamina; Diethanolamin; Diethanolamine; Diolamina; Diolaminum; Диоламин.

Bis(2-hydroxyethyl)amine; 2,2'-Iminobisethanol.

$C_4H_{11}NO_2$=105.1

CAS — 111-42-2.

UNII — AZE05TDV2V.

Pharmacopoeias. In *USNF.*

USNF 31: (Diethanolamine). It is a mixture of olamines, consisting largely of diolamine. White or clear, colourless crystals, deliquescing in moist air, or a colourless liquid. Miscible with water, with alcohol, with acetone, with chloroform, and with glycerol; slightly soluble to insoluble in ether, in petroleum spirit, and in benzene. Store in airtight containers. Protect from light.

Profile

Diolamine is an organic base that is used as an emulsifier and dispersant.

It is used to solubilise fusidic acid and sulfafurazole by the formation of the diolamine salt. It has been used for the preparation of salts of iodinated organic acids used as contrast media. It may be irritating to the skin and mucous membranes.

Dioxan

Diethylene Dioxide; Diethylene Ether; Dioksaan; Dioksaani; Dioksan; Dioxane; 1,4-Dioxano; Dioxano; 1,4-Dióxido de dietileno; Éter de dietileno; Диоксан.

1,4-Dioxane.

$C_4H_8O_2$=88.11

CAS — 123-91-1.

UNII — J8A3510O7S.

NOTE. Do not confuse dioxan and dioxin (p. 2494.2).

Description. Dioxan is a colourless flammable liquid with an ethereal odour. Wt per mL about 1.03 g. B.p. about 101 degrees. Store in airtight containers.

Stability. It is dangerous to distil or evaporate dioxan unless precautions have been taken to remove explosive peroxides.

Uses

Dioxan is used as an industrial solvent.

Adverse Effects, Treatment, and Precautions

Dioxan vapour is irritant to mucous membranes. High concentrations may cause nausea and vomiting, and CNS depression with headache, dizziness, drowsiness, and in severe cases unconsciousness. On repeated exposure, severe hepatic and renal damage, including necrotic changes, can occur and may be fatal. Direct contact with liquid dioxan can result in dermatitis. Dioxan has been shown to be carcinogenic in *animals*.

Treatment consists of removal from exposure and general supportive and symptomatic measures.

Handling. Suitable precautions should be taken to avoid skin contact with dioxan as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Dioxan is absorbed after inhalation and through the skin. It is metabolised by oxidation to β-hydroxyethoxy-acetic acid.

Emulsifying Waxes

Cera emulgente; Cera Emulsificans; Cera emulsionante; Cetylanum; Emulsif. Wax; Эмульгирующий Воск.
CAS — 8014-38-8.

Pharmacopoeias. *Br., Eur.* (see p. vii), and *USNF* all have monographs for different emulsifying waxes.

Ph. Eur. 8: (Cetostearyl Alcohol (Type A), Emulsifying; Alcohol Cetylicus et Stearylicus Emulsificans A). A mixture containing not less than 80% cetostearyl alcohol and not less than 7% sodium cetostearyl sulfate, both calculated with reference to the anhydrous substance. A suitable buffer may be added. White or pale yellow, waxy mass, plates, flakes, or granules. Soluble in hot water giving an opalescent solution: practically insoluble in cold water; slightly soluble in alcohol.

Ph. Eur. 8: (Cetostearyl Alcohol (Type B), Emulsifying; Alcohol Cetylicus et Stearylicus Emulsificans B). A mixture containing not less than 80% cetostearyl alcohol and not less than 7% sodium laurilsulfate, both calculated with reference to the anhydrous substance. A suitable buffer may be added. White or pale yellow, waxy mass, plates, flakes, or granules. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; slightly soluble in alcohol.

BP 2014: (Emulsifying Wax; Anionic Emulsifying Wax). It is prepared from 9 parts of cetostearyl alcohol and 1 part of sodium laurilsulfate or sodium salts of similar sulfated higher primary aliphatic alcohols. An almost white or pale yellow, waxy solid or flakes, becoming plastic when warmed. Practically insoluble in water, forming an emulsion; partly soluble in alcohol.

BP 2014: (Cetomacrogol Emulsifying Wax; Non-ionic Emulsifying Wax). It is prepared from 4 parts of cetostearyl alcohol and 1 part of macrogol cetostearyl ether (22). A white or almost white, waxy solid or flakes melting when heated to a clear almost colourless liquid. Practically insoluble in water, producing an emulsion; moderately soluble in alcohol; partly soluble in ether.

USNF 31: (Emulsifying Wax). It is prepared from cetostearyl alcohol containing a polyoxyethylene derivative of a fatty acid ester of sorbitan. M.p. 50 degrees to 54 degrees. It is a creamy-white, wax-like solid, with a mild characteristic odour. Insoluble in water; soluble in alcohol; freely soluble in chloroform, in ether, in most hydrocarbon solvents, and in aerosol propellants.

Profile

Emulsifying waxes are mixtures of fatty alcohols with surfactants. They are mainly based on cetostearyl alcohol (p. 2178.1) and can be classified as anionic, cationic, or nonionic depending on the surfactant used (see Emulsifying and Solubilising Agents, p. 2164.1). Pharmacopoeias may use the name Emulsifying Wax for either anionic or nonionic forms, and nomenclature may therefore be confusing.

Emulsifying waxes are used to produce oil-in-water emulsions that are stable over a wide pH range; their compatibilities depend on the surfactant used. Added to fatty or paraffin bases they produce preparations that are absorbed and nongreasy when rubbed into the skin. They are a constituent of hydrophilic ointment bases for so called washable ointments, and are also used in rectal preparations, and in cosmetics.

Sunscreen activity. Emulsifying ointment, which contains emulsifying wax with white soft paraffin and liquid paraffin, was found to have major sunscreen activity in clinically normal skin.[1] It should not be used before phototherapy or in phototesting procedures.

1. Cox NH, Sharpe G. Emollients, salicylic acid, and ultraviolet erythema. *Lancet* 1990; 335: 53–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Epaderm; Epaderm; *Irl.*: Silcocks Base; *Malaysia*: Aqua Cream; *UK*: Epaderm; Hydromol.

Pharmacopoeial Preparations
BP 2014: Aqueous Cream; Emulsifying Ointment.

Eosin

CI Acid Red 87; Colour Index No. 45380; D & C Red No. 22; Eosin Y; Eosina; Éosine Disodique; Eozin; Eozyna; Эозин.
The disodium salt of 2',4',5',7'-tetrabromofluorescein .
$C_{20}H_6Br_4Na_2O_5$=691.9
CAS — 548-26-5; 17372-87-1.
ATC — D08AX02.
ATC Vet — QD08AX02.
UNII — TDQ283MPCW.

Pharmacopoeias. In *Fr.*

Uses

The name eosin is used for a range of red synthetic dyes that are derivatives of bromofluorescein. It is most commonly used for Eosin Y, the tetrabromo derivative, but Eosin B, the dibromodinitro derivative, has also been widely used.

Eosin has been incorporated in solution-tablets to give a distinctive colour to solutions prepared from them. It is also used in cosmetics.

Eosin has been used as a topical antiseptic in nappy rash, burns and other skin conditions, although other drugs are usually preferred.

Adverse Effects

Hypersensitivity. Contact dermatitis associated with the use of eosin in cosmetics such as lipsticks was once relatively common but the incidence decreased with reduced use of eosin and the availability of purer forms. There have also been cases reported with topical application of antiseptic preparations containing eosin, which one report[1] suggested might be due to an impurity. However, another[2] implicated eosin itself after patch tests were performed with various products and pure tetrabromofluorescein.

1. Tomb RR. Allergic contact dermatitis from eosin. *Contact Dermatitis* 1991; 24: 27–9.
2. Koch P, *et al.* Allergic contact dermatitis from purified eosin. *Contact Dermatitis* 1995; 32: 92–5.

Epichlorohydrin

Epichloorhydrine; Epichlorhydrin; Epichlorohydryna; Epiclorhidrina; Эпихлоргидрин.
1-Chloro-2,3-epoxypropane.
C_3H_5ClO=92.52
CAS — 106-89-8.
UNII — 08OOR508C0.

Description. Epichlorohydrin is a colourless, flammable liquid. Wt per mL about 1.18 g. B.p. 115 degrees to 118 degrees. Store in airtight containers.

Stability. The vapour of epichlorohydrin forms explosive mixtures with air. Harmful gases including phosgene are liberated on heating of epichlorohydrin.

Uses

Epichlorohydrin is used as an industrial solvent.

Adverse Effects and Precautions

Epichlorohydrin is irritant. It has been shown to be carcinogenic in *animals*.

References to the toxicity of epichlorohydrin.

1. WHO. Epichlorohydrin. *Environmental Health Criteria 33*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc33.htm (accessed 30/06/04)
2. WHO. Epichlorohydrin health and safety guide. *IPCS Health and Safety Guide 8*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg008.htm (accessed 30/06/04)
3. Health and Safety Executive. Ammonia, 1-chloro-2,3-epoxypropane (epichlorohydrin), carcinogenicity of cadmium and its compounds. *Toxicity Review 24*. London: HMSO, 1991.
4. IARC/WHO. Epichlorohydrin. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; 71: 603–28. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)
5. Kolman A, *et al.* Genotoxic effects of ethylene oxide, propylene oxide and epichlorohydrin in humans: update review (1990–2001). *Mutat Res* 2002; 512: 173–94.

Handling. Suitable precautions should be taken to avoid skin contact with epichlorohydrin as it can penetrate skin and produce systemic toxicity.

Erythritol

Eritrit; Eritritolis; Érythritol; Erythritolum; Erytritol; Erytritoli; Erytrytol; *meso*-Erythritol; Tetrahydroxybutane; Эритрит.
(2*R*,3*S*)-Butane 1,2,3,4-tetrol.
$C_4H_{10}O_4$=122.1
CAS — 149-32-6.
UNII — RA96B954X6.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Erythritol). A white or almost white, crystalline powder or free-flowing granules. Freely soluble in water; very slightly soluble in alcohol.

USNF 31: (Erythritol). A white or almost white crystalline powder or free-flowing granules. Freely soluble in water; very slightly soluble in alcohol.

Profile

Erythritol is a sugar alcohol used as a sweetener and tablet diluent.

Erythrosine

CI Food Red 14; Colour Index No. 45430; E127; Eritrosin BS; Eritrosina; Eritrozin; Eritrozinas; Erythrosin; Érythrosine; Erythrosine BS; Erythrosine Sodium; Erytrosin; Erytrozyna; FD & C Red No. 3; Эритрозин.
The monohydrate of the disodium salt of 2',4',5',7'-tetraiodofluorescein .
$C_{20}H_6I_4Na_2O_5.H_2O$=897.9
CAS — 568-63-8 (anhydrous erythrosine sodium); 16423-68-0 (anhydrous erythrosine sodium); 49746-10-3 (erythrosine sodium monohydrate).
UNII — PN2ZH5LOQY.

Profile

Erythrosine is a synthetic dye used as a colouring agent for medicines, foods, and cosmetics. It is also used as a disclosing agent for plaque on teeth.

Although early *animal* studies had indicated that erythrosine might have an adverse effect on the thyroid gland, a review[1] of the evidence and later studies, suggested that erythrosine was not genotoxic or mutagenic and was suitable for use as a food colour. Similarly, no evidence was found to support restricting its use in pharmaceutical products.[2]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4*. London: HMSO, 1987.
2. European Commission. Opinion on toxicological data on colouring agents for medicinal products: erythrosin, adopted by the Scientific Committee on Medicinal Products and Medical Devices on 21 October 1998. Available at: http://ec.europa.eu/health/scientific_committees/emerging/opinions/scmpmd/scmp_out08_en.htm (accessed 23/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Revelplac; *Austral.*: DiscloGel; DiscloTabs; *Canad.*: Chrom-O-Red; *UK*: Ceplac.

Multi-ingredient Preparations. *Arg.*: Revelplac 2001.

Ethyl Acetate

Acetat d'etil; Acetato de etila; Acetato de etilo; Acetato di etile; Acetic Ether; Acetoxletano; Aethylis Acetas; Aethylium Aceticum; Essigsäureethylester; Éster etil acético; Éster etílico del ácido acético; Etanoato de etilo; Éter acético; Éthanoate d'éthyle; Ethyl Ethanoate; Ethylacetaat; Ethylacetat; Ethyl-acetát; Éthyle, acétate d'; Ethylis acetas; Etil asetat; Etil-acetát; Etilacetatas; Etilacetāts; Etylacetat; Etylu octan; Etyylisetaatti; Octan ethylnatý; Vinagre de nafta; Этилацетат.
$C_4H_8O_2$=88.11
CAS — 141-78-6.
UNII — 76845O8NMZ.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Ethyl Acetate). A colourless, clear, volatile liquid. Relative density 0.898 to 0.902. B.p. 76 degrees to 78 degrees. Soluble in water; miscible with alcohol, with acetone, and with dichloromethane. Store at a temperature not exceeding 30 degrees. Protect from light.

USNF 31: (Ethyl Acetate). A transparent, colourless, flammable liquid having a fragrant, refreshing, slightly acetous odour. Sp. gr. 0.894 to 0.898. Soluble in water; miscible with alcohol, with ether, and with fixed and volatile oils. Store in airtight containers at a temperature not exceeding 40 degrees.

Uses

Ethyl acetate is used as a flavour and solvent in pharmaceutical preparations. It is also used in industry as a solvent and as an extraction solvent in food processing.

Adverse Effects

Ethyl acetate is irritant to mucous membranes. High concentrations may cause CNS depression. Ethyl acetate may be implicated in volatile substance abuse (see under Toluene, p. 2216.3).

For discussion of neurotoxicity after occupational exposure to solvents and the absence of such an effect with ethyl acetate, see under Toluene, p. 2216.2.

Ethyl Cinnamate

Cinnamato de etilo; Cinnamate, d'éthyle; Ethylcinnamaat; Ethylcinnamat; Zimtsäureethylester; Этилциннамат.

Ethyl (*E*)-3-phenylprop-2-enoate.

$C_{11}H_{12}O_2$=176.21

CAS — 103-36-6.

UNII — C023P3M5JT.

Pharmacopoeias. In *Br.*

BP 2014: (Ethyl Cinnamate). A clear, colourless or almost colourless liquid with a fruity, balsamic odour. Practically insoluble in water; miscible with most organic solvents.

Profile

Ethyl cinnamate is used as a flavour and perfume; it is an ingredient of Tolu-flavour Solution (BP 2014).

Preparations

Pharmacopoeial Preparations

BP 2014: Tolu-flavour Solution.

Ethyl Lactate

Ethyllactat; Etilo, lactato de; Milchsäureethylester; Mleczan etylu; Этилактат.

$C_5H_{10}O_3$=118.1.

CAS — 97-64-3.

UNII — F3P750W8L.

Profile

Ethyl lactate is used in the flavouring of pharmaceutical preparations and foods. It is also used as a solvent.

Ethyl lactate has been applied topically in the treatment of acne vulgaris. It is reported to lower the pH within the skin thereby exerting a bactericidal effect.

Ethyl Oleate

Aethylis Oleas; Ethyle, oléate d'; Ethylis Oleas; Ethyloleat; Ethyl-oleat; Etil-oleat; Etiloleas; Etyloleat; Etyylioleaatti; Oleato de etilo; Этилолеат.

$C_{20}H_{38}O_2$=310.5

CAS — 111-62-6.

UNII — Z7Z439864Y.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Ethyl Oleate). A clear, pale yellow or colourless liquid. It consists of the ethyl esters of fatty acids, mainly oleic acid. It may contain a suitable antioxidant. Practically insoluble in water; miscible with alcohol, with dichloromethane, and with petroleum spirit (40 degrees to 60 degrees). Protect from light.

USNF 31: (Ethyl Oleate). It consists of esters of ethyl alcohol and high-molecular-weight fatty acids, principally oleic acid. A mobile, practically colourless liquid. Insoluble in water; miscible with alcohol, with vegetable oils, with liquid paraffin, and with most organic solvents. Store in airtight containers. Protect from light.

Incompatibility. Ethyl oleate dissolves some types of rubber and causes others to swell.

Profile

Ethyl oleate is used as an oily vehicle.

Ethyl Vanillin

Etilvanilina; Этилванилин.

3-Ethoxy-4-hydroxybenzaldehyde.

$C_9H_{10}O_3$=166.2

CAS — 121-32-4.

UNII — YC9ST449YJ.

Pharmacopoeias. In *USNF.*

USNF 31: (Ethyl Vanillin). Fine, white or slightly yellowish crystals with a vanilla-like odour. M.p. is between 76 degrees and 78 degrees. Soluble 1 in 100 of water at 50 degrees and 1 in 2 of alcohol; freely soluble in chloroform, in ether, and in solutions of alkali hydroxides. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Profile

Ethyl vanillin is used as a flavour and in perfumery to impart the odour and taste of vanilla.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Granugen†.

Ethylcellulose *(rINN)*

Cellulose Ethyl Ether; E462; Ethylcellulose; Ethylcellulosum; Ethylcelulosa; Etilcelluloze; Etilcelluloz; Etilcelulosa; Etylcelulosa; Etyliselluloosa; Этилцеллюлоза.

CAS — 9004-57-3.

UNII — 7Z8S9VYZ4B (ethylcellulose); H3UP11403C (ethylcellulose (7 cps)); 6I475159RA (ethylcellulose (50 cps)); 47MLBOF1MV (ethylcellulose (100 cps)).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Int.* Also in *USNF.*

Ph. Eur. 8: (Ethylcellulose). A partly *O*-ethylated cellulose. It contains 44 to 51% of ethoxy (-OC_2H_5) groups, calculated on the dried basis. A white to yellowish-white, odourless or almost odourless, powder or granular powder. Solutions of ethylcellulose may show a slight opalescence. Practically insoluble in water, in glycerol (85%), and in propylene glycol; soluble in dichloromethane and in a mixture of 20 parts alcohol and 80 parts toluene (w/w); slightly soluble in ethyl acetate and methyl alcohol.

USNF 31: (Ethylcellulose). A partly *O*-ethylated cellulose. It contains 44.0 to 51.0% of ethoxy groups, calculated with reference to the dried substance. A free-flowing white to light tan powder. Its aqueous suspensions are neutral to litmus. Insoluble in water, in glycerol, and in propylene glycol. Ethylcellulose containing less than 46.5% of ethoxy groups is freely soluble in chloroform, in methyl acetate, in tetrahydrofuran, and in mixtures of aromatic hydrocarbons with alcohol; ethylcellulose containing 46.5% or more of ethoxy groups is freely soluble in alcohol, in chloroform, in ethyl acetate, in methyl alcohol, and in toluene.

Profile

Ethylcellulose is used as a binder in tablets and as a coating material for tablets, granules, and microcapsules. It is also used as a thickening agent.

Preparations

Pharmacopoeial Preparations

USNF 31: Ethylcellulose Aqueous Dispersion; Ethylcellulose Dispersion Type B.

Ethylene Glycol Esters

Ethylene Glycol Distearate

Glycol Distearate (USAN).

1,2-Ethanediyl Octadecanoate.

$C_{38}H_{74}O_4$=595.0

CAS — 627-83-8.

UNII — 13W7MDN21W.

NOTE. The name Glycol Stearate has been used for various esters of ethylene glycol with stearic acid, including ethylene glycol distearate.

Ethylene Glycol Monopalmitostearate

Estearato de etilenglicol; Ethylene Glycol Monostearate; Ethylene Glycol Stearate; Ethylène Glycol (Stéarate d'); Éthylèneglycol, monopalmitostéarate d'; Ethyleneglycoli Monopalmitostearas; Ethylenglycoli Monopalmitostearas; Ethylenglycoli Monostearas; Ethylenglycolmonopalmitostearat; Ethylenglykol-monopalmitostearat; Ethylení Glycoli Stearas; Etilenglicol, monopalmitoestearato de; Etilenglikolio monopalmitosztearas; Etilenglikol-monopalmitát-és-monosztearát; Etyleeniglykolimonopalmitostearaatti; Etylenglykol-monopalmitostearat; Monoéstearato de etilenglicol; Этиленгликоль моноацилмонопальмитостеарат.

CAS — 111-60-4 (ethylene glycol monostearate); 4219-49-2 (ethylene glycol monopalmitate); 91031-31-1 (ethylene glycol C16-C18 fatty acid esters).

UNII — 0324G66D0E.

Pharmacopoeias. In *Eur.* (see p. vii). *USNF* includes Ethylene Glycol Stearates.

Ph. Eur. 8: (Ethylene Glycol Monopalmitostearate). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid and not more than 5% of free ethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54 degrees to 60 degrees. Protect from light.

USNF 31: (Ethylene Glycol Stearates). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54 degrees to 60 degrees. Store in airtight containers.

Profile

Ethylene glycol distearate and monopalmitostearate are glycol ester nonionic surfactants (p. 2164.2) used as emulsion stabilisers, emollients, and opacifying agents; they have similar properties to glyceryl stearates (p. 2187.1). Ethylene glycol monolaurate and mono-oleate have also been used.

Ethylenediamine

Edamina; Edamine; Edamine (USAN); Edamine (pINN); Edaminum; Ethyleendiamine; Ethylendiamin; Ethylendiaminum; Ethylènediamine; Ethylenediaminum; Etilén-diamin; Etilendiamina; Etilendiaminas; Etilendiammina; Etilenodiamina; Etyleenidiamiini; Etylendiamin; Etylenodiamina; Эламин.

$C_2H_8N_2$=60.10

CAS — 107-15-3 (anhydrous ethylenediamine); 6780-13-8 (ethylenediamine monohydrate).

UNII — 60V9STC53F.

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

Ph. Eur. 8: (Ethylenediamine). A clear, colourless or slightly yellow, hygroscopic liquid. On exposure to air, white fumes are evolved. On heating it evaporates completely. Miscible with water and with alcohol. Store in airtight containers. Protect from light.

USP 36: (Ethylenediamine). A clear, colourless or only slightly yellow liquid having an ammonia-like odour. It is strongly alkaline and may readily absorb carbon dioxide from the air to form a non-volatile carbonate. Miscible with water and with alcohol. Store in well-filled, airtight, glass containers.

Uses and Administration

Ethylenediamine or ethylenediamine hydrate forms a stable mixture with theophylline to produce aminophylline or aminophylline hydrate. Ethylenediamine is widely used in the chemical and pharmaceutical industries and as an ingredient of some topical creams.

Adverse Effects

Ethylenediamine is irritant to the skin and to mucous membranes. Severe exfoliative dermatitis has been reported after systemic use of preparations containing ethylenediamine. Hypersensitivity reactions are common. Concentrated solutions cause skin burns. Headache, dizziness, shortness of breath, nausea, and vomiting have also been reported after exposure to fumes. Ethylenediamine splashed onto the skin or eyes should be removed by flooding with water for a prolonged period.

Precautions

Skin reactions may occur in patients given aminophylline after they have become sensitised to ethylenediamine. Cross-sensitivity with edetic acid and with some antihistamines has been reported.

Cross-sensitivity. It was reported that some topical corticosteroid creams, including *Tri-Adcortyl* in the UK,[1] and

Kenacomb, *Haicicomb*, and *Viaderm* in Canada,[2] contained ethylenediamine and could cause unexpected cross-sensitivity reactions with piperazine[1] or aminophylline.[2]

1. Wright S, Harman RRM. Ethylenediamine and piperazine sensitivity. *BMJ* 1983; 287: 463–4.
2. Hogan DJ. Excipients in topical corticosteroid preparations in Canada. *Can Med Assoc J* 1989; 141: 1032.

Ferric Oxide

Demir Oksitler; E172 (iron oxides or hydroxides); Eisen(III)-oxid; Ferri Oxidum Flavum (yellow ferric oxide); Ferri Oxidum Fuscum (brown ferric oxide); Ferri Oxidum Nigrum (black ferric oxide); Ferri Oxidum Rubrum (red ferric oxide); Ferrum Oxydatum Flavum (yellow ferric oxide); Ferrum Oxydatum Fuscum (brown ferric oxide); Ferrum Oxydatum Nigrum (black ferric oxide); Ferrum Oxydatum Rubrum (red ferric oxide); Hierro, óxido de; IJzer(III)oxide; Järn(III)oxid; Ossido Ferrico; Oxid Železitý; Óxido de Ferro (III); Óxido Férrico; Oxyde Ferrique; Rauta(III)oksidi; Tlenek Żelaza(III); Vas(III)-oxid; Оксид Железа.

CAS — 51274-00-1; 1309-37-1.

UNII — 1K09F3G675 (ferric oxide red); EX438O2MRT (ferric oxide yellow).

Pharmacopoeias. *Chin.* includes red, black, brown, purple, and yellow ferric oxide. *It.* includes both red and yellow ferric oxide. *USNF* allows the basic colours of red or yellow ferric oxide or mixtures of these.

USNF 31: (Ferric Oxide). A powder exhibiting two basic colours (red and yellow), or other shades produced on blending the basic colours. Insoluble in water and in organic solvents; dissolves in hydrochloric acid upon warming, a small amount of insoluble residue usually remaining.

Profile

Ferric oxide is used for colouring medicines, contact lenses, cosmetics, and foodstuffs.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Herbadict; *Rus.*: Liv 52 (Лив 52); *Ukr.*: Liv 52 (Лив 52).

Formamide

Carbamaldehído; Carbamaldehyde; Formamid; Formamida; Metanamida; Methanamide; Формамид.

CH_3NO=45.04

CAS — 75-12-7.

UNII — 4781T907ZS.

Description. Formamide is a colourless, oily liquid. B.p. 210 degrees. Wt per mL, about 1.13 g.

Profile

Formamide is used as an industrial solvent. It is reported to be irritant.

Gastric Mucin *(BAN)*

Mucina gástrica; Муцин; Желудочная Слизь.

Profile

Gastric mucin is a high-molecular-weight glycoprotein precipitated by alcohol (60%) after digestion of the stomach linings of hogs by pepsin and hydrochloric acid. It is used in artificial saliva formulations for dry mouth (p. 2175.3) as an oral spray containing 3.5% or as lozenges.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Neth.*: Saliva Orthana; *UK*: AS Saliva Orthana; AS Saliva Orthana.

Gellan Gum

E418; Gellángumi; Goma gellan; Gomme gellane; Геллановая Камедь.

CAS — 71010-52-1.

UNII — 7593U0914D.

Pharmacopoeias. In *USNF*.

USNF 31: (Gellan Gum). A high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with *Pseudomonas elodea*, purified by recovery with isopropyl alcohol, and then dried and milled. It is a heteropolysaccharide comprising a tetrasaccharide repeating unit of one rhamnose, one glucuronic acid, and two glucose units. The glucuronic acid is neutralised to mixed potassium, sodium, calcium, and magnesium salts. It may contain acyl (glyceryl and acetyl) groups as the *O*-glycosidically linked esters. An off-white powder. Soluble in hot or in cold deionised water.

Profile

Gellan gum is a sphingan polysaccharide produced by the bacterium *Pseudomonas elodea* (*Sphingomonas elodea*). It is used to produce gels and as a stabilising and suspending agent in pharmaceutical preparations. It is also used in the food and cosmetics industries.

References.

1. Fialho AM, *et al.* Occurrence, production, and applications of gellan: current state and perspectives. *Appl Microbiol Biotechnol* 2008; 79: 889–900.

Gentisic Acid Ethanolamide

Etanolamida del ácido gentísico.

2,5-Dihydroxybenzoic acid ethanolamide.

$C_9H_{11}NO_4$=197.2

CAS — 61969-53-7.

UNII — H4E039OIGX.

Profile

Gentisic acid ethanolamide has been used as a complexing agent in the manufacture of pharmaceutical preparations.

Glycerol Formal

Formaldehyde Glycerol; Glycérol formal; Glycerol-formalum; Methylene Glycerin; Глицерол Формаль.

A mixture of the two isomers 4-hydroxymethyl-1,3-dioxolane and 5-hydroxy-1,3-dioxane present in a constant ratio of 40:60 respectively.

$C_4H_8O_3$=104.1

CAS — 4740-78-7 (5-hydroxy-1,3-dioxane); 5464-28-8 (4-hydroxymethyl-1,3-dioxolane).

UNII — 3L7GR2604E (glycerol formal); F6UP32GBII (5-hydroxy-1,3-dioxane); Q45U46I791 (4-hydroxymethyl-1,3-dioxolane).

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

Ph. Eur. 8: (Glycerol Formal). A clear, colourless liquid. Miscible with water and with alcohol. Store under nitrogen, in airtight containers.

Profile

Glycerol formal is used as a pharmaceutical solvent.

Glyceryl Behenate

Behenin; Behenoylglycerol; Docosanoin; Glicerol, behenato de; Глицерил Бегенат.

1,2,3-Propanetriol docosanoate.

CAS — 77538-19-3 (glyceryl behenate); 30233-64-8 (glyceryl monobehenate); 99880-64-5 (glyceryl dibehenate); 18641-57-1 (glyceryl tribehenate).

UNII — R8WTH25YS2.

NOTE. The name docosanoin has been used for glyceryl behenate; distinguish from docosanol (p. 974.3), which is behenyl alcohol.

Pharmacopoeias. In *USNF*. *Eur.* (see p. vii) includes Glycerol Dibehenate.

Ph. Eur. 8: (Glycerol Dibehenate; Glyceroli Dibehenas). A mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols. It contains 15 to 23% of monoacylglycerols, 40 to 60% of diacylglycerols, and 21 to 35% of triacylglycerols, obtained by esterification of glycerol and behenic acid. A hard, waxy mass or powder or white or almost white, unctuous flakes. Practically insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane. M.p. 65 degrees to 77 degrees.

USNF 31: (Glyceryl Behenate). A mixture of glycerides of fatty acids, mainly behenic acid. A fine powder with a faint odour. M.p. about 70 degrees. Practically insoluble in water and in alcohol; soluble in chloroform. Store in airtight containers at a temperature not exceeding 35 degrees.

Profile

Glyceryl behenates are glycerol ester nonionic surfactants (p. 2164.2). They are used as lubricants, binders, and coatings in tablet-making, including modified-release oral preparations, and as emollients and emulsifiers in creams and lotions. They are also used in foods and cosmetics.

Glyceryl Mono- and Di-esters

E471 (mono- and di-glycerides of fatty acids); Glycerol Mono- and Di-esters; Mono- and Di-glycerides; Monos y diglicéridos; Моно- и Диглицериды.

Pharmacopoeias. In *USNF*.

USNF 31: (Mono- and Di-glycerides). A mixture of glycerol mono- and di-esters, with minor amounts of tri-esters, of fatty acids from edible oils. It contains not less than 40% of monoglycerides. It may contain suitable stabilisers. Store in airtight containers. Protect from light.

Profile

Glyceryl mono- and di-esters are mixtures of the glycerol esters of edible fatty acids. They are glycerol ester nonionic surfactants (p. 2164.2) and are used as emulsifying agents and food additives. Mixtures containing varying proportions of mono-, di-, and tri-esters are available and have differing properties; specific mixtures containing mainly esters of a single fatty acid are also used. Self-emulsifying forms (self-emulsifying mono- and diglycerides of food fatty acids) containing a small amount of soap or another surfactant are available for some of these mixtures; self-emulsifying glyceryl stearate is a commonly used example (see Glyceryl Stearates, p. 2187.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Grassolind Neutral.

Glyceryl Monocaprylocaprate

Glycerol Monocaprylocaprate; Glyceroli Monocaprylocapras; Glycerolmonocaprylocaprat.

CAS — 91744-32-0 (C8-10 mono-, di- and triglycerides); 26402-22-2 (glyceryl monocaprate); 26402-26-6 (glyceryl monocaprylate).

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

Ph. Eur. 8: (Glycerol Monocaprylocaprate). A mixture of monoacylglycerols, mainly mono-*O*-octanoylglycerol and mono-*O*-decanoylglycerol, containing variable quantities of di- and triacylglycerols, obtained by direct esterification of glycerol with octanoic and decanoic acids, followed by a distillation step in the case of glycerol monocaprylocaprate (type II). Content of glycerol monocaprylocaprate (type I): monoacylglycerols: 45 to 75%; diacylglycerols: 20 to 50%; triacylglycerols: maximum 10%. Content of glycerol monocaprylocaprate (type II): monoacylglycerols: minimum 80%; diacylglycerols: maximum 20%; triacylglycerols: maximum 5%. A colourless or slightly yellow, oily liquid or soft mass. Practically insoluble in water; very soluble in alcohol; freely soluble in dichloromethane.

Profile

Glyceryl monocaprylocaprate, a mixture of glyceryl caprate and glyceryl caprylate (p. 2562.3), is a glycerol ester nonionic surfactant (p. 2164.2). It is used as a solubiliser and emulsifier in pharmaceutical preparations.

Glyceryl Monolinoleate

Glicerin-monolinoleát; Glicerol, monolinoleato de; Glicerolio monolinoleatas; Glycerol Monolinoleate; Glycérol, monolinoléate de; Glyceroli monolinoleas; Glycerol-monolinolat; Glycerolmonolinoleat; Glyceryl Octadecadienoate; Glyserolimonolinoleaatti; Linoleoylglycerol; Monolinolein; Глицерилмонолинолеат.

CAS — 26545-74-4.

UNII — 4763AX184L.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Glycerol Monolinoleate). A mixture of monoacylglycerols, mainly mono-oleoylglycerol and mono-linoleoylglycerol, with variable quantities of di- and triacylglycerols. It contains 32 to 52% of monoacylglycerols, 40 to 55% of diacylglycerols, and 5 to 20% of triacylglycerols, obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of linoleic acid. A suitable antoxidant may be added.

Amber, oily liquids which may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane. Store in airtight containers. Protect from light.

USNF 31: (Glyceryl Monolinoleate). A mixture of monoglycerides, mainly glyceryl mono-oleate and glyceryl monolinoleate, with variable quantities of diglycerides and triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of linoleic acid. It contains 32 to 52% of monoglycerides, 40 to 55% of

diglycerides, and 5 to 20% of triglycerides. A suitable antoxidant may be added.

Amber, oily liquids that may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane; soluble in tetrahydrofuran. Store in airtight containers.

Profile

Glyceryl monolinoleate is a glycerol ester nonionic surfactant (p. 2164.2). It is used as an emulsifying and/or solubilising agent.

Glyceryl Mono-oleate

Glicerilo monooleato de; Glycerol Monooleate; Glycérol, monooléate de; Glyceroli monooleas; Glyceryl Monooleate; Glyceryl Octadecenoate; Monolein; Oleoylglycerol; Глицерилмоноолеат.

CAS — 2465-32-4

UNII — 4PC054V79P

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Glycerol Mono-oleates). Mixtures of monoacylglycerols, mainly mono-oleoylglycerol, with variable quantities of di- and triacylglycerols. They are defined by the nominal content of monoacylglycerols and obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of oleic acid, or by esterification of glycerol by oleic acid. A suitable antoxidant may be added.

Amber, oily liquids which may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane. Store in airtight containers. Protect from light.

USNF 31: (Glyceryl Monooleate). A mixture of monoglycerides, mainly glyceryl mono-oleate, with variable quantities of di- and triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of oleic acid, or by esterification of glycerol with oleic acid of vegetable or animal origin. It is defined by the nominal content of monoglycerides. A suitable antoxidant may be added.

Amber, oily liquids that may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane; soluble in tetrahydrofuran. Store in airtight containers.

Profile

Glyceryl mono-oleate is a glycerol ester nonionic surfactant (p. 2164.2). It has similar properties and uses to glyceryl monostearate or self-emulsifying glyceryl monostearate (below).

Glyceryl Stearates

Glycerol Octadecanoates; Glycerol Stearates; Stearoylglycerols.

Glyceryl Distearate

Distearoylglycerol; Glicerin-disztearát; Glicerol, diestearato de; Glicerolio distearatas; Glycerol Distearate; Glycérol, distéarate de; Glyceroldistearat; Glycerol-distearát; Glyceroli distearas; Glyserolidistearaatti; Глицеридистеарат.

CAS — 1323-83-7.

UNII — 730719MW2KM.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Glycerol Distearate). A mixture of diacylglycerols, mainly distearoylglycerol, with variable quantities of mono- and triacylglycerols. It contains 8 to 22% of monoacylglycerols, 40 to 60% of diacylglycerols, and 25 to 35% of triacylglycerols, obtained by partial glycerolysis of vegetable oils containing triacylglycerols of palmitic and stearic acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

A hard, waxy mass or powder, or white or almost white, unctuous flakes. Practically insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane. M.p. 50 degrees to 60 degrees (types I and II) or 50 degrees to 70 degrees (type III).

USNF 31: (Glyceryl Distearate). A mixture of diglycerides, mainly glyceryl distearate, with variable quantities of monoglycerides and triglycerides. It contains 8 to 22% of monoglycerides, 40 to 60% of diglycerides, and 25 to 35% of triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of palmitic or stearic acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

Hard, waxy mass or powder, or white or almost white flakes. Insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane and in tetrahydrofuran. Store in airtight containers.

Glyceryl Monostearate

Glicerilo monoestearato de; Glicerin-monosztearát; Glicerolio monostearatas; Glicerolu monostearynian; Glycerol, monostéarate de; Glyceroli monostearas; Glycerolimonostearat; Glycerol-monostearát; Glyserolimonostearaatti; GMS; Monoestearato de glicerilo autoemulsionable (Self-emulsifying Glyceryl Monostearate); Monostearin; Monostearin Emulsificans (Self-emulsifying Glyceryl Monostearate); Monostearoylglycerol; Глицеринмоностеарат.

CAS — 31566-31-1 (glyceryl monostearate); 26657-96-5 (glyceryl monopalmitate).

UNII — 230OU9XXE4 (glyceryl monostearate); 6Y2XJ0583S (glyceryl monopalmitate).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF. Br.* also includes Self-emulsifying Glyceryl Monostearate.

Ph. Eur. 8: (Glycerol Monostearate 40-55). A mixture of monoacylglycerols, mainly monostearoylglycerol, with variable quantities of di- and triacylglycerols. It contains 40 to 55% of monoacylglycerols, 30 to 45% of diacylglycerols, and 5 to 15% of triacylglycerols, obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of palmitic or stearic acid, or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

A white or almost white, hard, waxy mass or unctuous powder or flakes. Practically insoluble in water; soluble in alcohol at 60 degrees. M.p. 54 degrees to 66 degrees.

USNF 31: (Glyceryl Monostearate). It contains not less than 90% of monoglycerides of saturated fatty acids, chiefly glyceryl monostearate ($C_{21}H_{42}O_4$ = 358.6) and glyceryl monopalmitate ($C_{19}H_{38}O_4$ = 330.5). It may contain a suitable antoxidant.

A white to yellowish wax-like solid, beads, flakes, or powder with a slight, agreeable, fatty odour. M.p. not below 55 degrees. Insoluble in water but may be dispersed in hot water with the aid of a small amount of soap or other suitable surfactant; soluble 1 in 10 of chloroform, 1 in 100 of ether and of methyl alcohol, 1 in 33 of isopropyl alcohol; dissolves in hot organic solvents such as alcohol, acetone, mineral or fixed oils, and benzene. Store in airtight containers. Protect from light.

BP 2014: (Self-emulsifying Glyceryl Monostearate). A mixture consisting principally of mono-, di-, and triglycerides of stearic and palmitic acids, and of minor proportions of other fatty acids; it may also contain free fatty acids, free glycerol, and soap. It contains not less than 30% of monoglycerides, not more than 7% of free glycerol, and not more than 6% of soap, calculated as sodium oleate, all calculated with reference to the anhydrous substance.

A white to cream-coloured, hard, waxy solid with a faint fatty odour. Dispersible in hot water; soluble in hot dehydrated alcohol and in hot liquid paraffin; soluble in hot vegetable oils, but may give turbid solutions at concentrations below 20%.

Incompatibility. Because of the presence of soap, self-emulsifying glyceryl monostearate is incompatible with acids and high concentrations of ionisable salts, hard water, calcium compounds, zinc oxide, and oxides of heavy metals.

Glyceryl Palmitostearate

Glicerol, palmitoestearato de.

A mixture of mono-, di-, and triglycerides of C_{16} and C_{18} fatty acids.

CAS — 8067-32-1; 68002-71-1 (C16-18 glycerides).

UNII — GSY51O183C.

Profile

Glyceryl stearates are glycerol ester nonionic surfactants (p. 2164.2). They include a range of mixtures of glycerol mono-, di-, and tri-esters with palmitic and stearic acids and are used as emulsifiers and stabilisers in pharmaceuticals, foods, and cosmetics. They also have emollient properties.

Glyceryl monostearate is used as an emulsifying agent, emollient, and tablet and capsule lubricant. It is a poor water-in-oil emulsifier but is a useful stabiliser of water-in-oil and oil-in-water emulsions and can be included in preparations for internal or external use. A self-emulsifying form, which contains a small amount of soap or other surfactant, is also available. This can produce satisfactory oil-in-water emulsions and is used as an emulsifier for oils, fats, solvents, and waxes in the preparation of bases of the non-emulsified, emulsified, and vanishing-cream types. It is not intended for internal use and aqueous preparations containing it should also contain a preservative to prevent fungal or bacterial growth.

Glyceryl distearate and glyceryl tristearate (tristearin; tristearoylglycerol) have similar properties and uses to the monostearate. Glyceryl palmitostearate is used mainly as a diluent, lubricant, and modified-release agent for tablets and capsules.

Glycofurol

Glicofurol; Glycofural; Glycofurol 75; Tetrahydrofurfuryl Alcohol Polyethylene Glycol Ether; Гликофурфурол.

α-(Tetrahydrofurfuryl)-ω-hydroxypoly(oxyethylene).

$C_4H_7O(C_2H_4O)_nOH$

CAS — 9004-76-6; 31692-85-0.

UNII — YZC5LZ88UR.

Description. Glycofurol is a clear, colourless, almost odourless liquid. Wt per mL about 1.08 g. B.p. 80 degrees to 100 degrees. Incompatible with oxidising agents. Store under nitrogen in airtight containers. Protect from light.

Profile

Glycofurol is used as a pharmaceutical solvent for injections.

Green S

Acid Brilliant Green BS; Acid Green S; Briljantzuurgroen BS; Brillantsäuregrün BS; CI Food Green 4; Colour Index No. 44090; E142; Grün S; Grün S; Lissamine Green; Verde Brillante BS; Verde Lisamina; Verde S; Vert acide brillant BS; Vert lissamine Wool Green B; Zaliasis S; Yeşil S; Zieleń Brylantowa BS; Zielen S; Zöld S; Зеленый S.

Sodium 1-[4-dimethylamino-α-(4-dimethyliminiocyclohexa-2,5-dienylidene)benzyl]-2-hydroxynaphthalene-3,6-disulphonate.

$C_{27}H_{25}N_2NaO_7S_3$ = 576.6

CAS — 3087-16-9.

UNII — 9B7E8Y9D0X.

Uses

Green S is a synthetic triarylmethane dye used as a colouring agent in medicines, cosmetics, and foodstuffs. Strips impregnated with green S are used to stain the cornea to detect abnormalities.

References.

1. Bernsten DA, *et al.* Reliability of grading lissamine green conjunctival staining. *Cornea* 2006; 25: 695–700.
2. Korb DR, *et al.* An evaluation of the efficacy of fluorescein, rose bengal, lissamine green, and a new dye mixture for ocular surface staining. *Eye Contact Lens* 2008; 34: 61–4.
3. Machado LM, *et al.* Staining patterns in dry eye syndrome: rose bengal versus lissamine green. *Cornea* 2009; 28: 732–4.

Adverse Effects

Studies in *animals* indicated that there is some absorption of green S and caecal enlargement but it was considered that there is a very large margin of safety between the highest estimated human intake of green S of 130 micrograms daily and the level at which changes were seen in *animal* studies (500 mg/kg daily). It was recommended that the use of green S in food is acceptable.[1]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FAAC/REP/4.* London: HMSO, 1987.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA:* Green Glo.

Guaraprolose (rINN)

Guar Gum Hydroxypropyl Ether; Guaraprolosa; Guaraprolosum; HP-Guar; Hydroxypropyl Guar; 2-Hydroxypropyl Guar Gum; Hydroxypropyl Guar Gum; Гидроксипропил Гуар; Гуапропоза.

(1→6)-α-D-Galactopyrano-(1→4)-β-D-mannopyranan 2-hydroxypropyl ether.

$[C_{18}H_{30}O_{15}(C_3H_6O)_x]_n$

CAS — 39421-75-5.

Profile

Guaraprolose is a nonionic thickening agent derived from guar gum (p. 475.1) that is used in eye drops for the management of dry eye conditions. It also used in skin and hair care products and has many industrial applications.

References.
1. Petricek I, *et al.* Hydroxypropyl-guar gellable lubricant eye drops for dry eye treatment. *Expert Opin Pharmacother* 2008; 9: 1431–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Systane; *Irl.*: Systane; *UK*: Systane.

Multi-ingredient Preparations. *Braz.*: Mirugell; *Chile*: Systane; *Fr.*: Lubri-Mucal; Systane; *Ital.*: Systane; *Singapore*: Systane; *Thai.*: Systane.

Hard Fat

Adeps Neutralis; Adeps Solidus; Glicéridos semisintéticos sólidos; Glycérides hémi-synthétiques solides; Glycérides Semi-synthétiques Solides; Grasa sólida; Hårdfett; Hartfett; Kietieji riebalai; Kovarasva; Massa Estearínica; Neutralfett; Szilárd zsír; Tłuszcz obojętny; Tuk ztužený; Твёрдый Жир.
UNII — 8334LX7S21.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Hard Fat). A mixture of triglycerides, diglycerides, and monoglycerides obtained either by esterification of fatty acids of natural origin with glycerol or by transesterification of natural fats. A white or almost white, waxy, brittle mass. M.p. 30 degrees to 45 degrees; it does not differ by more than 2 degrees from the nominal value. Practically insoluble in water; slightly soluble in dehydrated alcohol. When heated to 50 degrees, it melts giving a colourless or slightly yellowish liquid. Protect from light and heat.

USNF 31: (Hard Fat). A mixture of glycerides of saturated fatty acids. A white mass, almost odourless and free from rancid odour, and greasy to the touch. M.p. is between 27 degrees and 44 degrees and does not differ by more than 2 degrees from the nominal value. The melted substance is colourless or slightly yellowish and forms a white emulsion when shaken with an equal amount of hot water. Practically insoluble in water; slightly soluble in alcohol; freely soluble in ether. Store in airtight containers at a temperature 5 degrees or more below the melting-point.

Profile

Hard fat is a name applied to a range of bases with varying degrees of hardness and differing melting ranges used for the preparation of suppositories and vaginal pessaries. Hard fat is also used in some topical preparations.

Hard Paraffin

Cera de parafina; Cera de petróleo; Hard Wax; Hartparaffin; Kietasis parafinas; Paraff. Dur.; Paraffin; Paraffin, fast; Paraffin Wax; Paraffine solide; Paraffinum Durum; Paraffinum solidum; Parafiini, kiinteä; Parafin tvrdý; Parafina sólida; Parafina stała; Szilárd paraffin; Твёрдый Парафин.
CAS — 8002-74-2.
UNII — I9O0E3H2ZE.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

USNF also includes Synthetic Paraffin.

Ph. Eur. 8: (Paraffin, Hard). A purified mixture of solid saturated hydrocarbons, generally obtained from petroleum. M.p. 50 degrees to 61 degrees. It is a colourless or white mass. The melted substance is free from fluorescence in daylight. Practically insoluble in water and in alcohol; freely soluble in dichloromethane. Protect from light.

USNF 31: (Paraffin). A purified mixture of solid saturated hydrocarbons obtained from petroleum. It may contain suitable antoxidants. It is a colourless or white, odourless, more or less translucent mass showing a crystalline structure, and is slightly greasy to the touch. It has a congealing range of 47 degrees to 65 degrees. Insoluble in water and in alcohol; slightly soluble in dehydrated alcohol; freely soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils. An alcoholic extract is neutral to litmus. Store at a temperature not exceeding 40 degrees. Protect from light.

USNF 31: (Synthetic Paraffin). A very hard odourless white wax containing mostly long-chain, unbranched, saturated hydrocarbons, with a small amount of branched hydrocarbons. The average molecular weight may range from 400 to 1400. Insoluble in water; very slightly soluble in aliphatic, oxygenated, and halogenated hydrocarbon solvents; slightly soluble in aromatic and normal paraffinic solvents.

Profile

Hard paraffin is used mainly as a stiffening agent in ointment bases. It is also used in creams, and as a coating for capsules and tablets.

Hard paraffin is used in physiotherapy in the form of paraffin-wax baths for the relief of pain in inflamed joints and sprains.

The injection of paraffins may produce granulomatous reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Melrose; *USA*: DermaPhor.

Pharmacopoeial Preparations
BP 2014: Paraffin Ointment; Simple Ointment; Wool Alcohols Ointment.

Hexachloroethane

Carbon Hexachloride; Heksakloorietaani; Hexachloorethaan; Hexachlorethan; Hexachloroéthane; Hexacloretano; Hexacloruro de carbono; Hexacloruro de etano; Hiiliheksakloridi; Perchloorethaan; Perchloroethane; Percloroetano; Perkloorietaani; Гексахлорэтан.
C_2Cl_6=236.7
CAS — 67-72-1.
UNII — G30K3QQT4J.

Profile

Hexachloroethane is a chlorinated hydrocarbon used in industry as a solvent. Eye irritation and photophobia have resulted from industrial exposure to the vapour. It was formerly used in veterinary medicine as an anthelmintic, but has been superseded by less toxic drugs.

n-Hexane

n-Esano; *n*-Heksaani; *n*-Heksan; *n*-Heksáns; *n*-Hekzan; *n*-Hexà; *n*-Hexaan; *n*-Hexan; *n*-Hexán; *n*-Hexano; Hexano normal; Hidruro de hexilo; н-Гексан.
C_6H_{14}=86.18
CAS — 110-54-3.
UNII — 2DDG612ED8.

Description. *n*-Hexane is a colourless, flammable, volatile liquid with a faint odour. Wt per mL about 0.66 g. B.p. about 69 degrees. Store in airtight containers.

Uses

n-Hexane is widely used as an industrial solvent, as a solvent in glues, and as an extraction solvent in food processing.

Adverse Effects

n-Hexane is irritant. Acute exposure to the vapour may result in CNS depression with headache, drowsiness, dizziness, and in severe cases unconsciousness. Chronic occupational exposure and abuse of *n*-hexane have been associated with the development of peripheral neuropathies. *n*-Hexane is a constituent of some adhesives and may be implicated in volatile substance abuse (see under Toluene, p. 2216.3). Some adverse effects of petrol have been attributed to its content of *n*-hexane.

References.
1. Health and Safety Executive. *n*-Hexane. *Toxicity Review 18.* London: HMSO, 1987.
2. WHO. *n*-Hexane. *Environmental Health Criteria 122.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc122.htm (accessed 30/06/04)
3. WHO. *n*-Hexane health and safety guide. *IPCS Health and Safety Guide 59.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg059.htm (accessed 30/06/04)

Effects on the nervous system. There have been many reports of peripheral neuropathy attributed to the abuse of, and occupational exposure to, *n*-hexane, although symptoms tend to be milder in the latter.[1] Tetraplegia has occurred in severe cases. There is typically a clinical deterioration several weeks after exposure followed by a slow recovery which, in severe cases, may not be complete. It has been suggested that methyl ethyl ketone potentiates the peripheral neuropathy induced by *n*-hexane. Occupational exposure to *n*-hexane has also been associated with cranial nerve neuropathy.

Parkinsonism in a leather worker, possibly associated with exposure to solvents, mainly *n*-hexane, has been noted.[2]

For further discussion of neurotoxicity after occupational exposure to solvents including *n*-hexane, see under Toluene, p. 2216.2.

1. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; 8: 293–300.
2. Pezzoli G, *et al.* Parkinsonism due to n-hexane exposure. *Lancet* 1989; ii: 874.

Pharmacokinetics

n-Hexane is absorbed after inhalation and to a limited extent through the skin. Oxidative metabolites, including 2,5-hexanedione are excreted in the urine largely as conjugates. Some unchanged *n*-hexane is excreted via the lungs.

Hexylene Glycol

Hexilenglicol; Гександиол.
2-Methyl-2,4-pentanediol.
$C_6H_{14}O_2$=118.2
CAS — 107-41-5.
UNII — KEH0A3F75J.

Pharmacopoeias. In *USNF.*

USNF 31: (Hexylene Glycol). A clear, colourless, viscous liquid. Absorbs moisture when exposed to moist air. Miscible with water and with many organic solvents including alcohol, acetone, chloroform, ether, and hexanes. Store in airtight containers.

Profile

Hexylene glycol has properties similar to those of propylene glycol (p. 2205.2). It is used as a solvent and humectant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA*: Bodi Kleen.

Hydrogenated Polydecene

E907; Hydrogenated Polydec-1-ene; Hydrogenated Poly-α-olefin; INS No. 907; Гидрогенизированный Полидецен.
CAS — 68037-01-4.
UNII — U333RI6EB7.

Pharmacopoeias. In *USNF.*

USNF 31: (Hydrogenated Polydecene). A mixture of saturated, synthetic hydrocarbons in the range $C_{30}H_{62}$ to $C_{70}H_{142}$, made from direct oligomerisation of 1-decene (C_{10} alpha olefin). The oligomer mixture may be distilled to fractions of a suitable calculated viscosity and hydrogenated to reach saturation, or it may be hydrogenated to reach saturation and then distilled to the desired viscosity. It may contain a stabiliser. A clear, colourless, odourless, tasteless liquid. Very slightly soluble in water. Store in airtight containers.

Profile

Hydrogenated polydecene is used as an emollient, mainly in cosmetic preparations. It is also used as a coating agent in the food industry.

Hyetellose *(rINN)*

Hidroksietilcelulloze; Hidroxietilcelulóz; Hidroxietilcelulosa; Hydroksietyyliselluloosa; Hydroksyetylocelluloza; Hydroxietylcellulosa; Hydroxyethyl Cellulose; Hydroxyethylcellulose; Hydroxyéthylcellulose; Hydroxyethylcellulosum; Hyetellose; Hyetellosum; Hyetelosa; Idrossietilcellulosa; Гиетеллоза.
CAS — 9004-62-0.
UNII — 8136Y38GY5 (hyetellose (140 cps at 5%)).

NOTE. **HECL** is a code approved by the BP 2014 for use on single unit doses of eye drops containing hyetellose and sodium chloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Hydroxyethylcellulose). A partially substituted 2-hydroxyethyl ether of cellulose. Various grades are available and are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% solution measured at 25 degrees. A white, yellowish-white, or greyish-white, powder or granules. Soluble in cold or hot water, forming colloidal solutions; practically insoluble in alcohol, in acetone, and in toluene. A 1% solution in water has a pH of 5.5 to 8.5.

USNF 31: (Hydroxyethyl Cellulose). A partially substituted poly(hydroxyethyl) ether of cellulose. It is available in several grades, varying in viscosity and degree of substitution, and some grades are modified to improve

their dispersion in water. It may contain suitable anticaking agents. A white to light tan, practically odourless, hygroscopic, powder. Soluble in cold or hot water, giving a colloidal solution; practically insoluble in alcohol and in most organic solvents. pH of a 1% solution in water is between 6.0 and 8.5.

Profile

Hyetellose is used in pharmaceutical manufacturing as a thickener and stabiliser and as a tablet coating and binding agent. It is present in lubricant preparations for dry eye (p. 2190.1), contact lens care (p. 1730.2), and dry mouth (p. 2175.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Goniosol†; *Israel*: Celluspan; Lyteers; V-Tears; *USA*: Comfort Tears; TearGard†.

Multi-ingredient Preparations. *Arg.*: Hidratagel†; *China*: Le Dun Qing (乐敦清); *Ger.*: Lubricano; *Irl.*: Minims Artificial Tears; *Israel*: Lacrimol; V-Crima; *Turk.*: Gleitgelen; *UK*: Minims Artificial Tears; *USA*: Biotene with Calcium; Mimyx†; Optimoist.

Hymetellose *(rINN)*

HEMC; Hidroxietilmetilcelulosa; Hydroxyethyl Methylcellulose; Hydroxyethylmethylcellulose; Hymétellose; Hymetellosum; Methylhydroxyethylcellulose; Methylhydroxyethylcellulose; Methylhydroxyethylcellulosum; Metilhidroksietilceliuloze; Metilhidroxietilcelulóz; Metylhydroxyetylcellulosa; Metyylihydroksietyyliselluloosa; Гипетеллоза.

CAS — 9032-42-2.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Methylhydroxyethylcellulose; Hydroxyethylmethylcellulose BP 2014). A partially substituted ether of cellulose containing methoxyl and 2-hydroxyethyl groups. Various grades are available and are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20 degrees. A white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Practically insoluble in hot water, in dehydrated alcohol, in acetone, and in toluene; dissolves in cold water forming a colloidal solution. A 1% w/w solution in water has a pH of 5.5 to 8.0.

USNF 31: (Hymetellose). A partly *O*-(methylated) and *O*-(2-hydroxyethylated) cellulose. Various grades are available, labelled with the viscosity of a 2% w/w solution measured at 20 degrees. A white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Insoluble in hot water, in alcohol, in acetone, in ether, and in toluene; dissolves in cold water forming a colloidal solution. pH of a 1% w/w solution in water is between 5.5 and 8.0.

Profile

Hymetellose is used similarly to other cellulose ethers, such as methylcellulose (p. 2197.3), as a pharmaceutical excipient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Cellobexon.

Hyprolose *(rINN)*

E463; Hidroksipropilceliuloze; Hidroxipropilcelulóz; Hidroxipropilcelulosa; Hydroksipropyyliselluloosa; Hydroxipropylcellulosa; Hydroxypropyl Cellulose; Hydroxypropylcellulose; Hydroxypropylcellulosum; Hydroxypropylcelulosa; Hyprolosum; Гипролоза.

CAS — 9004-64-2.

UNII — REW2E1671P (hyprolose); 2165RE0K14 (hydroxypropyl cellulose, low-substituted).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn*. Also in *USNF* which has two separate monographs, for Hydroxypropyl Cellulose and for Low-substituted Hydroxypropyl Cellulose.

Ph. Eur. 8: (Hydroxypropylcellulose). A partially substituted 2-hydroxypropyl ether of cellulose. Various grades are available and may be distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20 degrees. White or yellowish-white, granules or powder; hygroscopic after drying. Soluble in cold water, in dehydrated alcohol, in glacial acetic acid, in methyl alcohol, in propylene glycol, and in a mixture of 10 parts methyl alcohol and 90 parts dichloromethane, forming colloidal solutions; practically insoluble in hot water, in ethylene glycol, and in toluene; sparingly soluble or slightly soluble in acetone. A 1% w/w solution in water has a pH of 5.0 to 8.5.

USNF 31: (Hydroxypropyl Cellulose). A partially substituted poly(hydroxypropyl) ether of cellulose. When dried at 105 degrees for 1 hour, it contains not more than 80.5% of hydroxypropoxy groups. It may contain not more than 0.60% of silica or other suitable anticaking agent. A white to cream-coloured, practically odourless, granular solid or powder, hygroscopic after drying. Soluble in cold water, in alcohol, in chloroform, and in propylene glycol, giving a colloidal solution; insoluble in hot water. pH of a 1% solution in water is between 5.0 and 8.0.

USNF 31: (Low-Substituted Hydroxypropyl Cellulose). It contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups. A white to yellowish-white, practically odourless, hygroscopic, fibrous or granular powder. Practically insoluble in dehydrated alcohol and in ether; dissolves in a solution of sodium hydroxide (1 in 10) and produces a viscous solution; swells in water, in sodium carbonate, and in 2N hydrochloric acid. pH of the suspension obtained by shaking 1.0 g with 100 mL of water is between 5.0 and 7.5. Store in airtight containers.

Uses and Administration

Hyprolose is used in pharmaceutical manufacturing in the film coating of tablets, as a tablet excipient, as a thickener, and in microencapsulation. It is used as an emulsifier and stabiliser in the food industry.

Hyprolose is also used as a modified-release solid ophthalmic insert in the management of dry eye (p. 2190.1).

Adverse Effects

Hyprolose used as a solid ocular insert may result in blurred vision and ocular discomfort or irritation, including hypersensitivity and oedema of the eyelids.

Hypersensitivity. Allergic contact dermatitis was reported in a patient, associated with the hyprolose present in the reservoir layer of a transdermal estradiol patch.[1]

1. Schwartz BK, Clendenning WE. Allergic contact dermatitis from hydroxypropyl cellulose in a transdermal estradiol patch. *Contact Dermatitis* 1988; **18**: 106–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Lacrisert; *Fin.*: Lacrisert†; *Fr.*: Lacrisert; *India*: Homex; *Neth.*: Lacrisert†; *Swed.*: Lacrisert†; *USA*: Lacrisert.

Pharmacopoeial Preparations
USP 36: Hydroxypropyl Cellulose Ocular System.

Hypromellose *(BAN, rINN)*

E464; Hidroxipropilmetilcelulosa; Hipromeliozė; Hipromelióz; Hipromelosa; Hipromeloz; HPMC; Hydroxypropyl Methylcellulose; Hydroxypropylmethylcellulose; Hypromelloosi; Hypromellos; Hypromellosum; Hypromelosa; Hypromeloza; Methyl Hydroxypropyl Cellulose; Methylcellulose Propylene Glycol Ether; Methylhydroxypropylcellulose; Methylhydroxypropylcellulosum; Гипромеллоза.

CAS — 8063-82-9; 9004-65-3.
ATC — S01KA02.
ATC Vet — QS01KA02.
UNII — 3NXW29V3WO.

NOTE. HPRM is a code approved by the BP 2014 for use on single unit doses of eye drops containing hypromellose 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: (Hypromellose). A methyl and hydroxypropyl mixed ether of cellulose It contains methoxy and hydroxypropoxy groups conforming to the limits for the types 1828, 2208, 2906, and 2910, calculated on the dried basis (see Labelling, below). A white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Dissolves in cold water, forming a colloidal solution; practically insoluble in hot water, in dehydrated alcohol, in acetone, and in toluene. A 1% w/w solution in water has a pH of 5.0 to 8.0.

USP 36: (Hypromellose). A methyl and hydroxypropyl mixed ether of cellulose It contains methoxy and hydroxypropoxy groups conforming to the limits for the types 1828, 2208, 2906, and 2910, calculated on the dried basis (see Labelling, below). A white to slightly off-white fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture; insoluble in dehydrated alcohol, in chloroform, and in ether.

Labelling. In Europe, grades of hypromellose are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20 degrees (e.g. hypromellose 4500). In the USA, they are distinguished by appending a number in which the first 2 digits represent the approximate percentage content of methoxy groups, and the third and fourth digits the approximate percentage content of hydroxypropoxy groups.

Hypromellose Acetate Succinate

HPMCAS; Hydroxypropylmethylcellulose Acetate Succinate; Shin-etsu AQOAT (AS-HF) (06081224); Shin-etsu AQOAT (AS-HG) (06081224).

CAS — 71138-97-1.

UNII — 24P2YXD2PW (16070722); 36BGF0E889 (12070923); 6N003M473W (06081224).

Pharmacopoeias. In *USNF*.

USNF 31: (Hypromellose Acetate Succinate). A mixture of acetic acid and monosuccinic acid esters of hypromellose. White to yellowish-white, slightly hygroscopic, powder or pills. It is odourless or has a faint, acetic acid-like odour. Practically insoluble in water, in dehydrated alcohol, in xylene, and in *n*-hexane. Dissolves in 1N sodium hydroxide. Addition of a mixture of dehydrated alcohol and dichloromethane (1:1) or of acetone, produces a clear or turbid viscous liquid. Store in tight containers.

Hypromellose Phthalate *(BANM, rINNM)*

Ftalāt hypromelosy; Ftalato de hidroxipropilmetilcelulosa; Ftalato de hipromelosa; Hipromeliozės ftalatas; Hipromelózftalát; Hipromelosa, ftalato de; HPMCP; Hydroxypropyl Methylcellulose Phthalate; Hypromellooisftalaatti; Hypromellose, Phtalate d'; Hypromellosephthalat; Hypromellosftalat; Hypromelósi phthalas; Methylhydroxypropylcellulose Phthalate; Methylhydroxypropylcellulosi Phthalas; Гипромеллозы фталат.

CAS — 9050-31-1.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Hypromellose Phthalate). A monophthalic acid ester of hypromellose containing methoxy, 2-hydroxypropoxy, and phthalyl groups. It contains 21.0 to 35.0% of phthalyl groups calculated with reference to the anhydrous substance. White or slightly off-white, free-flowing flakes or a granular powder. Practically insoluble in water and in dehydrated alcohol; very slightly soluble in acetone and in toluene; soluble in a mixture of equal volumes of acetone and methyl alcohol, and of dichloromethane and methyl alcohol. Store in airtight containers.

USNF 31: (Hypromellose Phthalate). A monophthalic acid ester of hypromellose. It contains methoxy, hydroxypropoxy, and phthalyl groups. It contains 21.0 to 35.0% of phthalyl groups, calculated on the anhydrous basis. Store in airtight containers. A white, odourless, powder or granules. Practically insoluble in water, in dehydrated alcohol, and in hexane; produces a viscous solution in a mixture of dehydrated alcohol and acetone (1:1), or in a mixture of methyl alcohol and dichloromethane (1:1); dissolves in 1N sodium hydroxide. Store in airtight containers.

Labelling. Different grades of hypromellose phthalate in the USA are distinguished by appending a number in which the first 2 digits represent the approximate percentage content of the methoxy groups, the next 2 digits the approximate percentage content of hydroxypropoxy groups, and the last 2 digits the approximate percentage content of the phthalyl groups. Another system of nomenclature involves appending a number which indicates the pH value (X 10) at which the polymer dissolves in aqueous buffer solutions; letters such as S or F may also be used to indicate grades of high molecular-weight or small particle size respectively.

Profile

Hypromellose has properties similar to those of methylcellulose (p. 2197.3). It is used in pharmaceutical manufacturing for film-coating tablets, as a tablet binder, as a modified-release matrix, and as an emulsifier, suspending agent, and stabiliser in topical gels and ointments. Hypromellose may also be used as an emulsifier and stabiliser in the food industry.

Hypromellose acetate succinate and hypromellose phthalate are used as coating agents, particularly for enteric-coating of tablets and granules and for the preparation of modified-release granules. They may also be used in film coating and as a coating to mask the unpleasant taste of some tablets.

Hypromellose is widely used clinically in ophthalmic solutions; it is preferred to methylcellulose since mucilages of hypromellose have greater clarity and usually contain

fewer undispersed fibres. Hypromellose is used to prolong the action of medicated eye drops and, either alone or with other viscosity-increasing agents, in artificial tears preparations for the management of dry eye (below); solutions containing 0.3 to 1% of hypromellose are commonly used. Solutions for contact lens care (p. 1730.2) and for lubricating artificial eyes contain similar concentrations. Hypromellose is also used intra-ocularly, usually as a 2% solution, as an adjunct in ophthalmic surgery (below) and concentrations of up to 2.5% may be used topically to protect the cornea during gonioscopy procedures.

Hypromellose has been included in artificial saliva preparations used in the management of dry mouth (p. 2175.3), but other drugs are usually preferred.

Dry eye. Dry eye is a chronic condition caused by a disturbance in tear function. It is associated with instability of the tear film covering the eye, which breaks up to leave dry spots rather than being maintained between blinks, and also with tear hyperosmolarity.

Tears consist of a slightly alkaline fluid that is spread across the eye by blinking and is lost via the lachrymal ducts or by evaporation. Mucus secreted by the conjunctiva is also required to maintain tear film stability and dry eye can result from reduced production of either tears or conjunctival mucus. Reduced tear secretion is common in the elderly, but also occurs in some systemic disorders or as an adverse effect of drugs such as those, like tricyclic antidepressants, that have antimuscarinic effects.

Tear film instability may also result from increased tear evaporation, for example due to corneal exposure in thyroid disease, or from lid, corneal, or other eye disorders.

The main symptoms of dry eye are discomfort, typically with a chronic gritty sensation, visual disturbances, and sometimes photophobia. Inflammation of the ocular surface develops and, if left untreated, corneal ulceration and eventual loss of sight may occur. Keratoconjunctivitis sicca is sometimes used as a synonym for dry eye[1] but may also refer to the corneal inflammation that results from severe dry eye in Sjögren's syndrome (see below).

Treatment of dry eye is mainly symptomatic. 'Artificial tears' preparations are the mainstay of therapy[2-5] and are generally based on lubricating or viscosity-increasing agents, although some also contain electrolytes similar to those found in natural tears. Eye drops containing hypromellose or other cellulose ethers (carmellose, hyetellose, methylcellulose), guaraprolose, polyvinyl alcohol, or povidone are widely used. Carbomer, in liquid gel formulations, and ointments containing soft or liquid paraffins are also used. A systematic review[6] found no evidence that any type of artificial tear or ocular lubricant was markedly better than others. Ointments have a longer duration of action than drops, but tend to blur the vision and are most suitable for use at night. Drops should be used as frequently as required, up to hourly or more often if necessary. Frequent use of eye drops may cause sensitivity to the preservative, in which case preservative-free preparations should be considered. An alternative in patients needing very frequent instillation of drops is a slow-release ophthalmic insert of hyprolose.

Another approach to treatment is to reduce tear loss, for example using moisture-retaining glasses or contact lenses. Punctal occlusion with gelatin rods or collagen implants blocks tear outflow and may be used diagnostically or for treatment. Drugs that stimulate tear production or alter tear composition have also been tried; these include diquafosol, ecabet, icomucret (15-HETE), and rebamipide. Mucus build-up due to reduced tear production may respond to topical mucolytics such as acetylcysteine or bromhexine. In severe dry eye use of autologous serum eye drops may be effective; surgical procedures may be necessary in some patients.

Dry eye is increasingly being recognised as an inflammatory disorder and topical immunosuppressants and anti-inflammatory drugs have been investigated. Topical ciclosporin may be of benefit in some patients with keratoconjunctivitis sicca,[7,8] and short-term topical corticosteroids have also been used. Tetracyclines may be effective where there is inflammation of the lipid-secreting meibomian glands in the lid margin.

Sjögren's syndrome is an auto-immune inflammatory disease mainly affecting the lachrymal and salivary glands; it is often secondary to an auto-immune disorder such as rheumatoid arthritis.[9] Patients typically present with dry eye and dry mouth, but extra-glandular symptoms such as arthritis, vasculitis, nephritis, and neuropathies may also occur. Treatment is mainly symptomatic,[10-12] using artificial tears and other topical therapies for dry eye and artificial saliva for dry mouth (see under Carmellose, p. 2175.3). Oral pilocarpine or cevimeline may be of benefit for both dry eye and dry mouth, but adverse effects may limit their use. Systemic treatment with corticosteroids and immunosuppressants may be required for patients with extra-glandular symptoms;[10-12] other approaches such as B-cell depletion using the anti-CD20 antibody rituximab are under investigation.[10-12]

1. Lemp MA, *et al.* The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007; 5: 75–92.
2. Lemp MA. Management of dry eye disease. *Am J Manag Care* 2008; 14 (suppl): S88–S101.
3. Pflugfelder SC, *et al.* Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007; 5: 163–78.
4. Jackson WB. Management of dysfunctional tear syndrome: a Canadian consensus. *Can J Ophthalmol* 2009; 44: 385–94.
5. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. *Clin Ophthalmol* 2009; 3: 405–12.
6. Doughty MJ, Glavin S. Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review. *Ophthalmic Physiol Opt* 2009; 29: 573–83.
7. Anonymous. Ophthalmic cyclosporine (Restasis) for dry eye disease. *Med Lett Drugs Ther* 2003; 45: 42–3.
8. Kymionis GD, *et al.* Treatment of chronic dry eye: focus on cyclosporine. *Clin Ophthalmol* 2008; 2: 829–36.
9. Fox RI. Sjögren's syndrome. *Lancet* 2005; 366: 321–31.
10. Ng KP, Isenberg DA. Sjögren's syndrome: diagnosis and therapeutic challenges in the elderly. *Drugs Aging* 2008; 25: 19–33.
11. Ramos-Casals M, *et al.* Treatment of primary Sjögren syndrome: a systematic review. *JAMA* 2010; 304: 452–60.
12. Becker H, *et al.* Emerging treatment strategies and potential therapeutic targets in primary Sjögren's syndrome. *Inflamm Allergy Drug Targets* 2010; 9: 10–9.

Ophthalmic surgery. Intra-ocular hypromellose may be used as a visco-elastic agent to protect the eye during surgery. In cataract extraction it is used to maintain the anterior chamber and to coat the intra-ocular lens to facilitate its implantation. Although intra-ocular hypromellose is generally considered to be well tolerated, some[1] have reported an increased incidence of pupil abnormalities (non-reactive semi-dilated pupils) after such use; others[2] did not confirm this. There has also been a report[3] of corneal opacities in several patients after use of intra-ocular hypromellose.

1. Tan AKK, Humphry RC. The fixed dilated pupil after cataract surgery—is it related to intraocular use of hypromellose? *Br J Ophthalmol* 1993; 77: 639–41.
2. Eason J, Seward HC. Pupil size and reactivity following hydroxypropyl methylcellulose and sodium hyaluronate. *Br J Ophthalmol* 1995; 79: 541–3.
3. Newton JN, *et al.* Corneal opacities after cataract surgery with hypromellose. *Lancet* 2000; 355: 290.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Artelac; Cool Tears; Genteal; Lacrigest; Lagrima Dorf; Latlas Tears; Lubrilag; Natura Lagrimas; Ocutears; Oftalook Plus; *Austral.*: Genteal; In A Wink Moisturising; *Austria*: Artelac; Okuzell†; Prosicca; *Belg.*: Artelac; Isopto Tears; *Braz.*: Artelac; Filmcel; Genteal; *Canad.*: Eyelube; Genteal; Isopto Tears; Lacril†; Visine Advance True Tears; Visine Contact Lens; *Chile*: Genteal; Luvis; Meticel; *Denm.*: Artelac Viskose øjendraber; *Fin.*: Artelac; Isopto Alkaline; Isopto Plain; *Fr.*: Artelac; Ocucoat†; *Ger.*: Artelac; Berberil Dry Eye; Cellugel; Celoftal; Genteal; Lacri-Vision; Methocel; Pan-Vision; Sic-Ophtal; Sicca-Stulln; *Gr.*: Hymecel; Lubrilac Vidilac; *Hong Kong*: Artears†; Blueye; Eye Glo Moist; Eye Mo Moist†; Genteal; Isopto Tears; Lac-Oph; Methopt†; *Hung.*: Humalac B; *India*: Aquaplus; Caresol; Erisol; Eyefil; Eyemist; Eysol; Genteal; Gonosol; Hymelose; Hyprosol†; Ilcleen; Intavisc; Lacrigel; Lub-Gel; Lubiziab; Moisol-Z; Moisol; Nova Vizol†; Optear; Sanvisc; *Indon.*: Genteal; *Irl.*: Artelac; Isopto Alkaline†; Isopto Plain†; *Israel*: Artelac; Genteal; Ocucoat†; *Ital.*: Gel 4000; Genteal; Lacrisifi; Lacrisol; Methocel; *Malaysia*: Cellugel†; Eye Glo Moist; Genteal; *Mex.*: Artelac; Celulose; Genteal; Lub Alvar; Luvistar; Meticel; *Neth.*: Artelac; *Norw.*: Artelac; *NZ*: Genteal; Methopt; *Philipp.*: Artears; Artelac; Genteal; Hypromax; Ilube; Itearz; Methopt; Opticul; Vistatears; *Pol.*: Artelac; *Port.*: Artelac; Davilose; *Rus.*: Defislez (Дефислёз); Lacrisifi (Лакрисифи); Lacrisyn (Лакрисин); *S.Afr.*: Cellugel†; Methocel†; Spersatear; Viscotraan; *Singapore*: Artelac; Eye Mo Moist; Genteal; Methocel; Optovisc; *Spain*: Acuolens; Artific; *Swed.*: Artelac; Isopto Plain; *Switz.*: Isopto Tears; Methocel; *Thai.*: Genteal; Isopto Tears†; Lac-Oph; Natear; Opsil Tears; Optal-Tears; *Turk.*: Lacrisifi; *UK*: Artelac; Brolene Cool Eyes; Hydromoor; Isopto Alkaline; Isopto Plain; Lumecare Tear Drops; *Ukr.*: Artelac (Артелак); *USA*: Artificial Tears; Entrocel†; Genteal; Gonak; Goniosoft; Goniosol; Isopto Plain; Isopto Tears; Lacril; Natural Balance Tears; Ocucoat; Tearisol; Tears Again MC; Ultra Tears†; *Venez.*: Genteal.

Multi-ingredient Preparations. *Arg.*: Alcon Lagrimas; Irix Lagrimas; *Kalopsis Lagrimas*; *Phoenix Lagrimas*; Prednifarma; Punto G†; Solucion Oral; Tears Naturale Forte; Tears Naturale†; Visine Lagrimas; *Austral.*: Bion Tears; Blink-N-Clean; Genteal; Poly-Tears; Tears Naturale; *Belg.*: Alcon Adequad; Lacrystat; Tears Naturale; *Braz.*: Lacribell; Lacrima Plus; Opti-Tears; Trisorb; *Canad.*: Artificial Tears†; Bion Tears; Clear Eyes for Dry Eyes Plus Redness Relief; Genteal Geldrops; Tears Naturale Forte; Tears Naturale; *Chile*: Kliner; Lagrimas Artificiales; Nico Drops; Nicotears; Novo-Tears; Tears Naturale; Tears Visine†; *China*: Bion Tears (倍然); Tears Naturale Forte (新倍然); Tears Naturale II (倍然II); *Cz.*: Tears Naturale; *Denm.*: Dacriosol; *Ger.*: Herba-Vision Augenbad; Herba-Vision Augentrost; Herba-Vision Blaubeere; Herba-Vision Kamille; Lacrisic; Oculotect; *Gr.*: Gastrovisol; Tearprol; Tears Naturale; *Hong Kong*: Bion Tears; Tears Naturale Forte; Tears Naturale; Visine for Contacts†; *Hung.*: Dacrolux; Tears Naturale; *India*: Binea; Decomic; Fixiflox-H; Flubip; Flurbiren; Irimist; Moisol; Nafilin; O-Dex; Ocuclear; *Indon.*: Genteal; Isotic Tearin; Tears Naturale II; Tears; *Irl.*: Ilube†; Physiotears†; Tears Naturale; *Israel*: Tears Natural; *Ital.*: Dacriosol; Pupilla Light; Tirs; *Malaysia*: Bion Tears; Dacrolux; Genteal; Tears Naturale; *Mex.*: Lacrima Plus; Naphacel; Naphtears; Naturalag; Splash Tears; Tears Naturale; *Neth.*: Duratears; Tears Naturale; *Norw.*: Tears Naturale; *NZ*: Poly-Tears; Tears Naturale; *Philipp.*: Gentle Tears; Tears Naturale; Visine Refresh; *Pol.*: Tears Naturale; *Rus.*: Tears Naturale (Слеза Натуральная); *S.Afr.*: Tears Naturale; *Singapore*: Bion Tears; Hair and Nails; Tears Naturale; *Spain*: Dacrolux; Humectante; Tears Humectante; *Swed.*: Bion Tears; *Switz.*: Herba-Vision Euphrasia; Herba-Vision Myrtillus; Tears Naturale; *Thai.*: Bion Tears†; Genteal; Opsar Tears; Tears Naturale; *Turk.*: Dacrolux; Tears Naturale; *UK*: Ilube; Murine Bright & Moist Eyes; Tears Naturale; Uvistat Eye Drops; *Ukr.*: Tears Naturale (Штучні Сльози)†; *USA*: Bion Tears; Clear Eyes CLR; Lacri-Tears; Lubri-Tears; Maximum Strength Allergy Drops; Moisture Drops; Nature's Tears; Ocucoat†; Tears Naturale; Tears Renewed†; Visine Maximum Redness Relief; Visine Pure Tears; Visine Tears; Visine Tired Eye Relief; Visine Totality Multi-Symptom Relief; *Venez.*: Genteal; OptiFresh.

Pharmacopoeial Preparations

BP 2014: Hypromellose Eye Drops;
USP 36: Hypromellose Ophthalmic Solution.

Isobutyl Alcohol

Alcohol isobutílico; 1-Hydroxymethylpropane; 1-Isobutanol; Isobutanol; Isopropylcarbinol; 2-Methylpropyl alcohol; Изобутиловый Спирт.

2-Methyl-1-propanol.

$C_4H_{10}O$=74.12

CAS — 78-83-1.

UNII — 56F9Z98TEM.

Pharmacopoeias. In *USNF.*

USNF 31: (Isobutyl Alcohol). A clear, colourless, mobile liquid. Soluble in water; miscible with alcohol, with ether, and with many other organic solvents. Store in airtight containers; avoid exposure to excessive heat above 40 degrees.

Profile

Isobutyl alcohol is used as an industrial solvent. It is also used as an anaesthetic in the American lobster, *Homarus americanus*.

References.

1. WHO. Butanols—four isomers: 1-butanol, 2-butanol, tert-butanol, isobutanol. *Environmental Health Criteria 65*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc65.htm (accessed 30/06/04)
2. WHO. Isobutanol health and safety guide. *IPCS Health and Safety Guide 9*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg009.htm (accessed 30/06/04)

Isopropyl Myristate *(USAN)*

Isopropyl myristát; Isopropyle, myristate d'; Isopropylis myristas; Isopropylmyristat; Isopropyylimyristaatti; Izopropil-mirisztát; Izopropilo miristatas; Izopropylu mirystynian; Miristato de isopropilo; Изопропилмиристат.

Tetradecanoic acid 1-methylethyl ester; Isopropyl tetradecanoate.

$C_{17}H_{34}O_2$=270.5

CAS — 110-27-0.

UNII — 0RE8K4LNJS.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Isopropyl Myristate). A clear, colourless, oily liquid. Relative density about 0.853. Immiscible with water; miscible with alcohol, with dichloromethane, with fatty oils, and with liquid paraffin. Protect from light.

USNF 31: (Isopropyl Myristate). A clear practically colourless, almost odourless, oily liquid; congeals at about 5 degrees. Insoluble in water, in glycerol and in propylene glycol; freely soluble in alcohol. Miscible with most organic solvents and with fixed oils. Store in airtight containers. Protect from light.

Incompatibility. Isopropyl myristate is incompatible with hard paraffin.

Uses

Isopropyl myristate is resistant to oxidation and hydrolysis and does not become rancid. It is absorbed fairly readily by the skin and is used as a basis for relatively nongreasy emollient ointments and creams. It is also used as a penetration enhancer for many substances applied externally as creams, sprays, or transdermal patches. A 50% application of isopropyl myristate has been used as a pediculicide.

Other isopropyl fatty acid esters, including di-isopropyl adipate, isopropyl laurate, isopropyl linoleate, and isopropyl palmitate (below) have similar pharmaceutical properties and are used in formulation for similar purposes to those of isopropyl myristate.

References.
1. Kaul N, *et al.* North American efficacy and safety of a novel pediculicide rinse, isopropyl myristate 50% (Resultz). *J Cutan Med Surg* 2007; 11: 161–7.

Adverse Effects

Hypersensitivity. A 64-year-old woman developed a rash[1] after using a sunscreen containing isopropyl myristate for 3 days, and patch testing confirmed a sensitivity both to this substance and to isohexadecane (a mixture of C_{16} paraffins).

1. Bharati A, King CM. Allergic contact dermatitis from isohexadecane and isopropyl myristate. *Contact Dermatitis* 2004; 50: 256–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Resultz; *Indon.*: Blue Cap; *Spain*: Nucoa†.

Multi-ingredient Preparations. *Canad.*: Secol; *Fr.*: Neuriplege Sport; *Gr.*: Hydromol; *India*: Aquasoft; Calyx; *Indon.*: Sodermix; *It.*: Diprobath; Emulsiderm; Hydromol; Hydromol; *Israel*: Emulsiderm; *UK*: Dermol; Diprobath†; Doublebase; Emulsiderm; Full Marks Solution; Hydromol; Hydromol; Soleve.

Isopropyl Palmitate

Isopropyl palmitat; Isopropyle palmitate d'; Isopropylis Palmitas; Isopropylpalmitat; Isopropyylipalmitaatti; Izopropilo palmitatas; Izopropil-palmitát; Palmitato de Isopropilo; Изопропилпальмитат.

Hexadecanoic acid 1-methylethyl ester; isopropyl hexadecanoate.

$C_{19}H_{38}O_2$ = 298.5

CAS — 142-91-6.

UNII — 8CRQ27H63M.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Isopropyl Palmitate). A clear, colourless, oily liquid. Relative density about 0.854. Immiscible with water; miscible with alcohol, with dichloromethane, with fatty oils, and with liquid paraffin. Protect from light.

USNF 31: (Isopropyl Palmitate). A colourless, mobile, liquid with a very slight odour. Insoluble in water, in glycerol, and in propylene glycol; soluble in alcohol, in acetone, in castor oil, in chloroform, in cottonseed oil, in ethyl acetate, and in mineral oil. Store in airtight containers. Protect from light.

Profile

Isopropyl palmitate has properties and pharmaceutical uses similar to those of isopropyl myristate (p. 2190.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Fotoprotector Isdin Extrem; *USA*: SalrStable Lo.

Kerosene

Cherosene; Fotogen; Keroseno; Kerosin; Kerosine; 'Paraffin'; Petrolej; Querosè; Querosene; Queroseno; Querosina; Žibalas; Керосин.

CAS — 8008-20-6.

UNII — 1C89KKCD4E.

NOTE. The nomenclature for kerosene and petroleum spirit (p. 2201.2) is confusing and not always clearly distinguishable; in many languages similar terms are used for both.

Description. Kerosene is a mixture of hydrocarbons, chiefly members of the alkane series, distilled from petroleum. It is a clear, colourless liquid with a characteristic odour. Sp. gr. about 0.8 g. B.p. 180 degrees to 300 degrees. An odourless grade is available. Store in airtight containers.

Uses

Kerosene is used as a degreaser and cleaner and as an illuminating and fuel oil in kerosene ('paraffin') lamps and stoves. The odourless grade has been used as a solvent in the preparation of some insecticide sprays.

Adverse Effects

The chief danger from ingestion of kerosene is pneumonitis and pulmonary complications resulting from aspiration. Spontaneous or induced vomiting increases the risk of aspiration. Ingestion of kerosene results in a burning sensation in the mouth and throat, gastrointestinal disturbances, and possibly cough, dyspnoea, and transient cyanosis. There may be excitation followed by CNS depression, with weakness, dizziness, drowsiness, confusion, incoordination, and restlessness progressing to convulsions, coma, and respiratory depression in severe cases. Cardiac arrhythmias have been reported.

The course of poisoning from inhalation is similar to that after ingestion although CNS and cardiac effects are more likely. Kerosene is irritant.

Abuse. Volatile substance abuse (p. 2216.3) involving inhalation and ingestion of kerosene has been reported.[1]

1. Das PS, *et al.* Kerosene abuse by inhalation and ingestion. *Am J Psychiatry* 1992; 149: 710.

Treatment of Adverse Effects

Treatment of kerosene poisoning is supportive and symptomatic. Every precaution should be taken to avoid aspiration of kerosene into the lungs. The UK National Poisons Information Service considers that gastric lavage should not be used. Adrenaline and other sympathomimetics may also be best avoided because of the risk of precipitating cardiac arrhythmias.

Laurocapram *(USAN, rINN)*

Azone; Laurocapramum; N-0252; Лаурокапрам.

1-Dodecylazacycloheptan-2-one; 1-Dodecylhexahydro-2*H*-azepin-2-one.

$C_{18}H_{35}NO$ = 281.5

CAS — 59227-89-3.

UNII — 7FJX9DRV9X.

Pharmacopoeias. In *Chin.*

Profile

Laurocapram has been investigated for enhancing the penetration of drugs through the skin.

References.
1. López-Cervantes M, *et al.* Chemical enhancers for the absorption of substances through the skin: Laurocapram and its derivatives. *Drug Dev Ind Pharm* 2006; 32: 267–86.

Liquid Paraffin

Aceite de parafina; Aceite de petróleo; Aceite de vaselina; Aceite mineral; Aceite mineral blanco; Dickflüssiges Paraffin; Folyékony paraffin; Heavy Liquid Petrolatum; Heavy Mineral Oil; Huile de Vaseline Épaisse; INS No. 905a; Liquid Petrolatum; Mineral Oil; Oleum Petrolei; Oleum Vaselini; Paraffin, flytande; Paraffin Oil; Paraffine liquide; Paraffinum Liquidum; Paraffinum Subliquidum; Parafiini, nestemäinen; Parafín tekutý; Parafina ciekła; Parafina líquida; Skystasis parafinas; Sıvı Parafin; Vaselinöl; Vaselinum Liquidum; White Mineral Oil; Медицинское Парафиновое Масло; Парафин Жидкий; Вазелиновое Масло; Жидкий Вазелин.

CAS — 8012-95-1.

ATC — A06AA01.

ATC Vet — QA06AA01.

UNII — T5L8T28FGP.

NOTE. The code 905 has been used for mineral hydrocarbons including liquid paraffin but E905 is now used specifically for microcrystalline wax (p. 2198.1).

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

Ph. Eur. 8: (Paraffin, Liquid). A purified mixture of liquid saturated hydrocarbons obtained from petroleum. It is a transparent, colourless, oily liquid, free from fluorescence in daylight. Relative density 0.827 to 0.890. Viscosity 110 to 230 mPa s. Practically insoluble in water; slightly soluble in alcohol; miscible with hydrocarbons. Protect from light.

USP 36: (Mineral Oil). A purified mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabiliser. It is a transparent, colourless, odourless or almost odourless, oily liquid, free, or practically free, from fluorescence. Insoluble in water and in alcohol; soluble in volatile oils; miscible with fixed oils (except castor oil). Store in airtight containers. Protect from light.

Light Liquid Paraffin

Dünnflüssiges Paraffin; Hígan folyó paraffin; Huile de Vaseline Fluide; Light Liquid Petrolatum; Light Mineral Oil; Light White Mineral Oil; Paraff. Liq. Lev.; Paraffin, lättflytande; Paraffine liquide légère; Paraffinum Liquidum Leve; Paraffinum Liquidum Tenue; Paraffinum Perliquidum; Parafiini, kevyt nestemäinen; Parafín tekutý lehký; Skystasis lengvas parafinas; Spray Paraffin; Vaselina líquida.

ATC — A06AA01.

ATC Vet — QA06AA01.

UNII — N6K5787QVP.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*. *US* also includes Topical Light Mineral Oil.

Ph. Eur. 8: (Paraffin, Light Liquid). A purified mixture of liquid saturated hydrocarbons obtained from petroleum. It is a transparent, colourless, oily liquid, free from fluorescence in daylight. Relative density 0.810 to 0.875. Viscosity 25 to 80 mPa s. Practically insoluble in water; slightly soluble in alcohol; miscible with hydrocarbons. Protect from light.

USNF 31: (Light Mineral Oil). A purified mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabiliser. It has similar characteristics to Mineral Oil but a lower kinematic viscosity. Store in airtight containers. Protect from light.

Uses and Administration

Taken orally, liquid paraffin acts as a lubricant and, since it keeps the stools soft, it has been used in the symptomatic treatment of constipation (p. 1804.3), although it should be used with caution because of its adverse effects. The recommended daily oral dose is 10 to 30 mL in divided doses, preferably before breakfast and at night. An emulsion of liquid paraffin may also be used in a dose of 10 to 30 mL at night. Liquid paraffin and its preparations should not, however, be taken immediately before going to bed. Liquid paraffin is an ingredient of several preparations that contain other laxatives such as cascara, magnesium hydroxide, or phenolphthalein. It has also been given as an enema in a usual dose of 120 mL.

Externally, liquid paraffin may be used as an ingredient of ointment bases, as an emollient and cleanser in certain skin conditions, and as an ophthalmic lubricant in the management of dry eye (p. 2190.1).

Light liquid paraffin has similar uses to liquid paraffin.

Administration in children. UK licensed product information gives the following oral doses of liquid paraffin for constipation in children, to be taken at night:

- under 3 years: not recommended
- 3 to 5 years: 2.5 to 5 mL
- 5 to 12 years: 5 to 10 mL
- over 12 years: as for adults

The Paediatric Formulary Committee considered doses of liquid paraffin preparations unsuitable for inclusion in the *BNFC 2009* and subsequent editions.

Adverse Effects and Precautions

Excessive oral or rectal dosage with liquid paraffin may result in anal seepage and irritation, excessive purgation, and watery diarrhoea. Liquid paraffin is absorbed to a slight extent and may give rise to foreign-body granulomatous reactions. Similar reactions have followed the injection of liquid paraffin and may be considerably delayed in onset. Injection may also cause vasospasm and prompt surgical removal may be required to prevent severe damage. Lipoid pneumonia has been reported after aspiration of liquid paraffin. Because of the risk of aspiration, oral liquid paraffin should not be given to patients who have difficulty swallowing, or to those with impaired neurodevelopment.

Some licensed product information warns that chronic ingestion of liquid paraffin may rarely be associated with impaired absorption of fat-soluble vitamins and possibly other compounds. There is little published evidence to support this. Prolonged use should, however, be avoided. Liquid paraffin should not be used when abdominal pain, nausea, or vomiting is present. The UK CSM considers that it should not be used in children under 3 years of age.

Granuloma. References.
1. Di Benedetto G, *et al.* Paraffin oil injection in the body: an obsolete and destructive procedure. *Ann Plast Surg* 2002; 49: 391–6.

Lipoid pneumonia. References.
1. Becton DL, *et al.* Lipoid pneumonia in an adolescent girl secondary to use of lip gloss. *J Pediatr* 1984; 105: 421–3.
2. Ohwada A, *et al.* Exogenous lipoid pneumonia following ingestion of liquid paraffin. *Intern Med* 2002; 41: 483–6.
3. Karacan O, *et al.* Fire-eater's pneumonia after aspiration of liquid paraffin. *Turk J Pediatr* 2006; 48: 85–8.
4. Meltzer E, *et al.* Lipoid pneumonia: a preventable complication. *Int Med Assoc J* 2006; 8: 33–5.
5. Corrin Y, *et al.* Exogenous lipid pneumonia. *Respiration* 2008; 76: 442–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Babix; Lansoyl; Lax Ewe Jalea†; Laxante Arceli; Laxuave Enteral; Laxuave Jalea; Lexavite; Lubritina Franklin†; Modaton NI; Oilatum; *Austral.*: Agarol; *Hamilton Dry Skin*: Hamilton Skin Active Urederm Cleanser; Oilatum Bar†; Oilatum Emollient†; Oilatum Shower Gel†; Parachoc; *Belg.*: Lansoyl; *Braz.*: Nujol; *Canad.*: Fleet Enema Mineral Oil; Lansoyl; Oilatum; *Chile*: Laxonarol; *Cz.*:

Oilatum Emollient; Oilatum Gel; *Fr.*: Lansoyl; Lubentyl; Oilatum Emollient; Restrical; *Ger.*: Obstinol M; *Gr.*: Agarol Plain; Nujol; Paragel; *Hong Kong*: Hamilton Body Wash†; Keri†; Oilatum Bar; Oilatum Emollient; Oilatum Gel; Vigarol†; *India*: Moyzen; Oilatum; *Indon.*: Oilatum Bar†; Oilatum Gel†; *Irl.*: Oilatum Gel; Oilatum Junior; Oilatum Soap; *Malaysia*: Balneum†; Egozite Protective Baby Lotion†; Oilatum; *Mon.*: Parlax; *NZ*: Fleet Mineral Enema†; Oilatum†; *Philipp.*: Oilatum; *Pol.*: Mentholaxin; Oilatum; *S.Afr.*: Oilatum Bar†; Oilatum Emollient†; *Singapore*: Balneum†; Laxarol; Oilatum Bar; Oilatum Emollient; Oilatum Gel; *Spain*: Emuliquen Simple; Hodermal; *Switz.*: Lansoyl; Laxamalt; Paragol N; *Thai.*: Agarol†; Oilatum Bar†; Oilatum Emollient†; Oilatum Gel†; *Turk.*: Duratears; Sokol; *UK*: Cetraben Emollient; Dermamist; Keri; LPL; Lyclear Treatment Shampoo; Oilatum Bath Formula; Oilatum Fragrance Free; Oilatum Gel; Oilatum Junior; Oilatum Soap; Zerobase; Zerolatum; *USA*: Kondremul; Liqui-Doss†; Min-O-Bar.

Multi-ingredient Preparations. *Arg.*: Agarol; Alcon Lagrimas; Aqualane; Mil-Par; Percutalfa; *Austral.*: Alpha Keri; Dermeze; Duratears; E45; Egozite Baby Cream; Epaderm; Granugen†; Hamilton Dry Skin; Hamilton Skin Active Urederm Cream; Ircal; Lacri-Lube; Oilatum Plus; Pinetarsol; QV Flare Up; QV Flare Up; Soov Prickly Heat; *Austria*: Balneum F; Neda Fruchtewurfel; *Belg.*: Duratears; Lacrytube; Transitol; *Braz.*: Agarol; Balmex; Parapsyl; *Canad.*: Agarol Plain; Akwa Tears; Duolube; Episec; Huile de Bain Therapeutique; Hypotears; Lotion Lubrifiante Calmante Hydratante†; Magnolax; Optilube; Refresh Lacri-Lube; Sebamed; Secol; Tears Naturale PM; *Chile*: Acnaid; Agarol†; Agarol; Cold Cream Avene; Durasolets; Duratears; Lacri-Lube; Vaselina Emulsionada; *Cz.*: Balmandol; Balneum Hermal F; Oilatum Plus; *Denm.*: Ojensalve Neutral; *Fin.*: Lacri-Lube; *Fr.*: Cerat Inalterable†; Cold Cream Naturel; Dexeryl; Lubentyl a la Magnesie; Melaxose; Parapsyllium; Transitol; Transulose; *Ger.*: Balneum F; Coliquifilm; Gleitgelen; Neuroderm; Oleobal; Vita-POS; *Gr.*: Duratears; Hydromol; *Hong Kong*: Duratears; Ego Skin Cream; Egozite Baby Cream; Oilatum Cream; Oilatum Plus; Polytar Emollient; Soov Prickly Heat; *Hung.*: Balneum Hermal F; *India*: Adlube; Agarol; Aquasoft; Asilax; Bajoffin; Bioffin; Calkem; Calosoft; Calvera; Calyx; Cetraben; Cimfi; Coslax; Creamee; Cremaffin Plus; Cremaffin; Daffolac-P; Dermoys; Dershine; Dewee; Diafoot; Duolaxin; Easylax; Elsoft; Elure; Emoderm; Foot Care; Gowet; Hidrate; *Himosf*; *Laxicare*; *Laxifin*; *Laxit Plus*; *Laxit*; *Leoben*; *Moisturex*; Moitz; Momplus; Moyzen; Novalax; Oilatum Plus; Oilatum; *Indon.*: Laxadine; Oilatum Plus†; Yanthi Baby Oil†; *Irl.*: Diprobath; Emulsiderm; Hydromol; Hydromol; Lacri-Lube; Milpar; Oilatum Cream; Oilatum Emollient; Oilatum Junior Flare-Up; Oilatum Plus; Polytar Emollient; *Israel*: Balneum F; CleanEars; Duratears; Emulsiderm; Lacrimol†; Vita-POS; *Ital.*: Balneum Hermal Forte; Duolaxan; Lacrilube; Transitol; Transulose; *Malaysia*: Aqua Cream; Balneum†; Duratears Naturale; Ego Skin Cream; Egozite Baby Cream; Lacrilube; Oilatum Plus Antibacterial; Oilatum; QV Flare Up†; *Mex.*: Acuafil Ungena; Milpar; Transilax; *Mon.*: Dermagor Betacade; *Neth.*: Duratears Z; Transulose; *Norw.*: Simplex; *NZ*: Alpha Keri; BK; DP Lotion - HC; DP; Ego Skin Cream; Egozite Baby; Hydroderm; Lacrilube; Oilatum Plus; Poly-Visc; Polytar Emollient†; *Philipp.*: CleanEars; Oilatum Plus; Oilatum; *Pol.*: Amfobase†; Balneum Hermal F†; Diprobase; E45; Mentho-Paraffinol; Oilatum Plus; Unibasis; *Port.*: Banholeum Gele; Betacade; Melaxose; *S.Afr.*: Oilatum Plus; *Singapore*: Balneum; Beagarol; Duratears; Ego Skin Cream; Egozite Baby Cream; Lacrilube†; Metanium Everyday Barrier; Oilatum Cream; Oilatum Plus; QV Flare Up; *Spain*: Aceite Acalorico; Emuliquen Laxante; Lubrifilm†; Vaselatum; *Switz.*: Antidry; Antidry; Balmandol; Balmed Hermal F; Coliquifilm; Dexeryl; Paragar; *Thai.*: Duratears; Emulax; Oilatum Cream†; Oilatum Plus†; *Turk.*: Balmandol; *UK*: 50:50; Alpha Keri; Cetraben Emollient; Dermalo; Dermol; Diprobase; Diprobath†; Doublebase; *Emollin*; Emulsiderm; *Epaderm*; Feminesse; Hydromol; Hydromol; Imuderm†; Infaderm; Lacri-Lube; Lubri-Tears†; Lyclear Mousse; Lyclear Spray; Mil-Par; Oilatum Cream; Oilatum Emollient; Oilatum Junior; Oilatum Plus; Polytar Emollient; VitA-POS; Zerocream; Zeroguent; *Ukr.*: Transuloza (Трансулоза); *USA*: Agoral; Akwa Tears†; Albolene; Alpha Keri; Aquaphor Healing Ointment; Aquaphor†; Bodi Care Lotion; Bodi Oil; Boudreaux's Butt Paste; DermaPhor; Desitin Creamy; Dry Eyes; Duratears Naturale; Geri-Silk; *Haley's M-O*; Hemorid For Women; Hemorid For Women; Hydrocerin; Hydrocerin; Hypotears; Lacri-Gel; Lacri-Lube; Lacticare; LubriFresh PM; LubriTears; Paladin; Palomar E; Puralube; Refresh Lacri-Lube; Refresh PM; Soothe Night Time; Soothe XP; Stye; Systane Nighttime; Tears Again; Tears Renewed†; Throat Discs; Vagisil; *Venez.*: Mil-Par; Oleoderm.

Pharmacopoeial Preparations

BP 2014: Cetomacrogol Emulsifying Ointment; Cetrimide Emulsifying Ointment; Emulsifying Ointment; Light Liquid Paraffin Eye Drops; Liquid Paraffin and Magnesium Hydroxide Oral Emulsion; Liquid Paraffin Oral Emulsion; Simple Eye Ointment; Wool Alcohols Ointment;

USP 36: Bland Lubricating Ophthalmic Ointment; Mineral Oil Emulsion; Mineral Oil, Rectal; Topical Light Mineral Oil.

Logwood

CI Natural Black 1; Colour Index No. 75290; Кампешевое Дерево (*Haematoxylon campechianum*).

CAS — 8005-33-2 (CI natural black); 517-28-2 (haematoxylin).

Profile

Logwood extract is a colouring agent derived from the logwood tree, *Haematoxylum (Haematoxylon) campechianum*. The logwood extract haematoxylin is used mainly as a histological stain. It is also used for colouring non-absorbable sutures.

References.

1. Titford M. The long history of hematoxylin. *Biotech Histochem* 2005; 80: 73–8.
2. Smith C. Our debt to the logwood tree: the history of hematoxylin. *MLO Med Lab Obs* 2006; 38: 18, 20–2.

Macrogol Cetostearyl Ethers

Ceteareth Compounds; Ceteth Compounds (Macrogol Cetyl Ethers); Macrogol, éteres cetoestearílicos de; Macrogol, ether cétostéarylique de; Macrogoli Aether Cetostearylicus; Makrogol-cetil-sztearil-éter; Makrogolcetostearyleter; Makrogolio cetostearilo eteris; Makrogolisetostearyylieetteri; Полиэтиленгликоля и Цетостеарилового Спирта Эфиры.

CAS — 68439-49-6.

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

Ph. Eur. 8: (Macrogol Cetostearyl Ether). A mixture of ethers of mixed macrogols with linear fatty alcohols, mainly cetostearyl alcohol. It may contain some free macrogols and it contains various amounts of free cetostearyl alcohol. The amount of ethylene oxide reacted with cetostearyl alcohol is from 2 to 33 units per molecule (nominal value). White or yellowish-white waxy, unctuous mass, pellets, microbeads, or flakes. Macrogol cetostearyl ether with low numbers of ethylene oxide units per molecule is practically insoluble in water; soluble in alcohol and in dichloromethane. Macrogol cetostearyl ether with higher numbers of ethylene oxide units per molecule is dispersible or soluble in water; soluble in alcohol and in dichloromethane. Macrogol cetostearyl ether solidifies at 32 degrees to 52 degrees. Store in airtight containers. The labelling states the amount of ethylene oxide reacted with cetostearyl alcohol (nominal value).

Cetomacrogol 1000 *(BAN, rINN)*

Cétomacrogol 1000; Cetomacrogolum 1000; Éter monocetílico de polietilenglicol 1000; Polyethylene Glycol 1000 Monocetyl Ether; Polyoxyethylene Glycol 1000 Monocetyl Ether; Кетомакрогол 1000; Цетомакрогол 1000.

CAS — 9004-95-9 (macrogol cetyl ethers); 68439-49-6 (macrogol cetostearyl ethers).

UNII — I835H2IHHX.

NOTE. The name Cetomacrogol 1000 (*BAN, INN*) refers to a macrogol 20 ether with cetyl (hexadecyl) alcohol. The name has also been used for macrogol ethers with either cetyl or cetostearyl alcohol, such as Cetomacrogol 1000 BP, a macrogol ether containing 20 to 24 oxyethylene groups in the polyoxyethylene chain prepared from either cetyl alcohol or cetostearyl alcohol. However, the more specific term macrogol cetostearyl ether (22) has replaced cetomacrogol 1000 in BP formulations.

Pharmacopoeias. In *Int.*

Incompatibility. Cetomacrogol has been reported to be incompatible with phenols and to reduce the antibacterial activity of quaternary ammonium compounds. Cetomacrogol may separate from solutions in the presence of a high concentration of electrolytes.

Polyoxyl 20 Cetostearyl Ether

Polioxil 20, éter cetoestearílico de; Полиоксиэтилендиола 20 и Цетостеариловой Кислоты Эфир.

CAS — 68439-49-6.

UNII — YRC528SWUY.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyoxyl 20 Cetostearyl Ether). A mixture of the monocetostearyl (mixed hexadecyl and octadecyl) ethers of mixed macrogols, the average polymer length being equivalent to 17.2 to 25.0 oxyethylene units. A cream-coloured waxy unctuous mass, melting, when heated, to a clear brownish-yellow liquid. Soluble in water, in alcohol, and in acetone; insoluble in petroleum spirit. A 10% solution in water has a pH of 4.5 to 7.5. Store at a temperature of 8 degrees to 15 degrees in airtight containers.

Profile

Macrogol cetostearyl ethers are mixtures of macrogol ethers with mainly cetyl (palmitic) and stearyl alcohol. They are macrogol alkyl ether nonionic surfactants (p. 2164.2) and are used as surfactants and emulsifiers. Macrogol cetostearyl ether (22) is used with cetostearyl alcohol (for example, in the form of Cetomacrogol Emulsifying Wax BP 2014) as an emulsifying agent for making oil-in-water emulsions that are unaffected by moderate concentrations of electrolytes and that are stable over a wide pH range. It is also used to disperse volatile oils in water to form transparent sols.

Preparations

Pharmacopoeial Preparations

BP 2014: Cetomacrogol Emulsifying Wax.

Macrogol/glycerol Esters

Macrogolglycerides; Polyoxylglycerides.

Behenoyl Macrogolglycerides

Behenoyl Polyoxylglycerides.

Pharmacopoeias. In *USNF.*

USNF 31: (Behenoyl Polyoxylglycerides). A mixture of mono-esters, di-esters, and tri-esters of glycerol and mono-esters and di-esters of polyethylene glycols. The polyethylene glycols used have a mean molecular weight of 400. It is produced by esterification of glycerol and polyethylene glycols with behenic acid. A waxy solid or fine powder. Dispersible in water; insoluble in alcohol; soluble in dichloromethane. Store in airtight containers at a temperature not exceeding 35 degrees. Protect from light, heat, and moisture.

Caprylocaproyl Macrogolglycerides

Glyceromacrogoli Octanodecanoates; Glyceromakrogol-oktanodekanoáty; Kaprylokaproylmakrogolglycerider; Kaprylokaproyylimakrogolglyseridit; Macrogolglycérides caprylocapriques; Macrogolglyceridorum Caprylocaprates; Macrogolglycerolcaprylocaprate; Macrogolglyceroli Caprylocapras; Makrogol-és glicerin-kaprilátok és kaprátok; Makrogolgliceridų kaprilokaproilatai.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Caprylocaproyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols with a mean relative molecular mass between 200 and 400. They are obtained by partial alcoholysis of medium-chain triglycerides using macrogol or by esterification of glycerol and macrogol with caprylic (octanoic) acid and capric (decanoic) acid or a mixture of glycerol esters and condensates of ethylene oxide with caprylic acid and capric acid. They may contain free macrogols. A pale-yellow, oily liquid. Dispersible in hot water, freely soluble in dichloromethane.

USNF 31: (Caprylocaproyl Polyoxylglycerides). A mixture of mono-esters, di-esters, and tri-esters of glycerol and mono-esters and di-esters of polyethylene glycols. The polyethylene glycols used have a mean molecular weight between 200 and 400. It is produced by partial alcoholysis of medium-chain triglycerides with polyethylene glycol, by esterification of glycerol and polyethylene glycol with caprylic acid and capric acid, or as a mixture of glycerol esters and ethylene oxide condensate with caprylic acid and capric acid. It may contain free polyethylene glycols. Pale yellow, oily liquids. Dispersible in hot water; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees to 30 degrees. Protect from light and moisture.

Lauroyl Macrogolglycerides

Glyceromacrogoli Laurates; Glyceromakrogol-laráty; Lauroyl Polyoxyglycerides; Lauroylmakrogolglycerider; Lauroyylimakrogoliglyseridit; Macrogolglycérides lauriques; Macrogolglyceridorum laurates; Macrogolglyceroli Lauras; Macrogolglycerollaurate; Macrogolglyceridorum Laurates; Makrogol-és glicerin-laurátok; Makrogolgliceridų lauratai; Makrogologlicerydów lauryniany.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Lauroyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols with a mean relative molecular mass between 300 and 1500. They are obtained by partial alcoholysis of saturated oils mainly containing triglycerides of lauric (dodecanoic) acid, using macrogol, or by esterification of glycerol and macrogol with saturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of these hydrogenated oils. A pale yellow waxy solid. Dispersible in hot water, freely soluble in dichloromethane.

USNF 31: (Lauroyl Polyoxylglycerides). A mixture of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycols. The polyethylene glycols used have a mean molecular weight between 300 and 1500. It is produced by partial alcoholysis of saturated oils, mainly containing triglycerides of lauric

acid with polyethylene glycols, by esterification of glycerol and polyethylene glycols with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with the fatty acids of the hydrogenated oils. It may contain free polyethylene glycols. Pale yellow, waxy liquids. Dispersible in hot water; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Linoleoyl Macrogolglycerides

Glyceromacrogoli Linoleates; Glyceromakrogol-linoleaty; Linoleoylmakrogolglyceridai; Linoleoylmakrogolglyseridit; Macrogolglycerides linoléiques; Macrogolglyceridorum Linoleates; Macrogolglyceroli Linoleas; Macrogolglyceroli-linoleat; Makrogol-és glicerin-linolátok; Makrogolgliceridu-linoleatai; Makrogologlicerydów linoleiniany.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Linoleoyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols. They are obtained by partial alcoholysis of an unsaturated oil mainly containing triglycerides of linoleic (*cis,cis*-9,12-octadecadienoic) acid, using macrogol with a mean relative molecular mass between 300 and 400, or by esterification of glycerol and macrogol with unsaturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of this unsaturated oil. An amber, oily liquid which may give rise to a deposit after prolonged periods at 20 degrees. Practically insoluble but dispersible in water; freely soluble in dichloromethane. Protect from light.

USNF 31: (Linoleoyl Polyoxylglycerides). A mixture of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycols. The polyethylene glycols have a mean molecular weight between 300 and 400. It is produced by partial alcoholysis of unsaturated oils, mainly containing triglycerides of linoleic acid, with polyethylene glycol, by esterification of glycerol and polyethylene glycol with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with the fatty acids of the unsaturated oils. It may contain free polyethylene glycols. Amber, oily liquids. May develop deposit after prolonged storage periods at 20 degrees. Practically insoluble but dispersible in water; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Oleoyl Macrogolglycerides

Macrogolglycerides oléiques; Macrogolglyceridorum oleates; Macrogolglyceroli Oleas; Macrogolglycerololeate; Oleoyl Polyoxylglycerides.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Oleoyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols. They are obtained by partial alcoholysis of an unsaturated oil mainly containing triglycerides of oleic (*cis*-9-octadecenoic) acid, using macrogol with a mean relative molecular mass between 300 and 400, or by esterification of glycerol and macrogol with unsaturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of this unsaturated oil. An amber oily liquid, which may give rise to a deposit after prolonged periods at 20 degrees. Practically insoluble but dispersible in water; freely soluble in dichloromethane. Protect from light.

USNF 31: (Oleoyl Polyoxylglycerides). A mixture of monoesters, di-esters, and tri-esters of glycerol and mono-esters and di-esters of polyethylene glycols. Polyethylene glycols used have a mean molecular weight between 300 and 400. It is produced by partial alcoholysis of unsaturated oils, mainly containing triglycerides of oleic acid, with polyethylene glycol, by esterification of glycerol and polyethylene glycol with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with fatty acids of the unsaturated oils. It may contain free polyethylene glycols. Amber, oily liquids. May develop deposit after prolonged storage at 20 degrees. Practically insoluble but dispersible in water; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Stearoyl Macrogolglycerides

Glyceromacrogoli Stearates; Glyceromakrogol-stearaty; Macrogolglyceridorum Stearas; Macrogolglycérides stéariques; Macrogolglyceridorum Stearates; Macrogolglyceroli Stearas; Macrogolglycerolstearat; Makrogol-és glicerin-sztearátok; Stearoilmakrogolgliceridai; Stearoylmakrogolglyceridet; Stearoylmakrogolglyseridit.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Stearoyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols with a mean relative molecular mass between 300 and 4000. They are obtained by partial alcoholysis of saturated oils containing mainly triglycerides of stearic (octadecanoic) acid, using macrogol, or by esterification of glycerol and macrogol with saturated fatty acids, or by mixture of glycerol esters and condensates of ethylene oxide with the fatty acids of these hydrogenated oils. A pale yellow waxy solid. Dispersible in warm water and in warm liquid paraffin; freely soluble in dichloromethane; soluble in warm anhydrous ethanol.

USNF 31: (Stearoyl Polyoxylglycerides). A mixture of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycols. The polyethylene glycols used have a mean molecular weight between 300 and 4000. It is produced by partial alcoholysis of saturated oils, mainly containing triglycerides of stearic acid, with polyethylene glycol, by esterification of glycerol and polyethylene glycol with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with the fatty acids of the hydrogenated oils. It may contain free polyethylene glycols. Pale yellow, waxy solids. Dispersible in warm water and in warm paraffin; soluble in warm methyl alcohol; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Profile

Macrogol/glycerol esters are mixtures of glycerol ester and macrogol ester nonionic surfactants (p. 2164.2) and consist of macrogol esters and glycerol esters of the same fatty acid. They are used as self-emulsifying and solubilising agents in oral and topical formulations. They are also used in foods and cosmetics.

Macrogol 6 Glyceryl Caprylocaprate

Glyceromacrogoli 6 Octanodecanoas; Glyceromakrogol-6-oktánodekanoát; Macrogol 6 Glycerol Caprylocaprate; Macrogol 6 glycérol, caprylocaprate de; Macrogol 6 glyceroli caprylocapras; Macrogol-6-glycerolcaprylocaprat; Makrogol 6-glicerin éterek kaprilátjai és kaprátjai; Makrogol-6-glycerolkaprylokaprat; Makrogoli-6-glyserolikaprylokapraatti; Makrogolio 6 glicerolio kaprilokapratas; PEG-6 Caprylic/capric Glycerides; Polyoxyethylene 6 Caprylic/capric Glycerides.
CAS — 361459-38-3; 68954-97-2.

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

Ph. Eur. 8: (Macrogol 6 Glycerol Caprylocaprate). A mixture of mainly mono- and di-esters of polyoxyethylene glycerol ethers mainly with caprylic (octanoic) and capric (decanoic) acids. The average number of moles of ethylene oxide reacted per mole of substance is 6. Macrogol 6 glycerol caprylocaprate may be obtained by ethoxylation of glycerol and esterification with distilled coconut or palm kernel fatty acids, or by ethoxylation of mono- and diglycerides of caprylic and capric acids. A pale yellow liquid. Partly soluble in water, freely soluble in castor oil, in glycerol, in isopropanol and in propylene glycol. Viscosity about 145 mPa s.

Profile

Macrogol 6 glyceryl caprylocaprate is an ethoxylated glycerol ester nonionic surfactant (p. 2164.2). It is used as a solubiliser and emulsifier and as an emollient in topical preparations.

Macrogol 20 Glyceryl Monostearate

Glyceromacrogoli 20 Monostearas; Glyceromakrogol-20-monostearát; Macrogol 20 Glycerol Monostearate; Macrogol 20 glycérol, monostéarate de; Macrogol 20 glyceroli monostearas; Macrogol-20-glycerolmonostearat; Macrogoli 20 Glycerol Monostearate; Macrogoli 20 Glyceroli Monostearas; Makrogol-20-glicerin-monosztearát; Makrogol-20-glycerolmonostearat; Makrogoli-20-glyserolimonostearaatti; Makrogolio 20 glicerolio monostearatas; Makrogolo-20-glicerolu monostearynian; PEG-20 Glyceryl Stearate.
CAS — 68153-76-4.
UNII — MJV0165YY8.

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

Ph. Eur. 8: (Macrogol 20 Glycerol Monostearate). Macrogol 20 glycerol monostearate is obtained by ethoxylation with ethylene oxide of different types of glycerol stearates, mainly Glycerol Monostearate 40–55. The number of moles of ethylene oxide reacted per mole of glycerol stearate is 20 (nominal value). A pale yellow, oily liquid or gel. Soluble in water at 40 degrees and above and in alcohol; practically insoluble in light liquid paraffin and in fatty oils. Relative density about 1.07. Protect from light.

Profile

Macrogol 20 glyceryl monostearate is an ethoxylated glycerol ester nonionic surfactant (p. 2164.2). It is used as an emulsifier and solubiliser in pharmaceuticals, foods, and cosmetics.

Macrogol 15 Hydroxystearate

Macrogol 15 hydroxystearate de; Macrogol-15-hydroxystearat; Macrogoli 15 Hydroxystearas; Makrogol-hydroxystearát; Makrogol-15-hydroxistearat; Makrogolio-15-hydroksistearaatti; Makrogolio 15 hidroksistearatas; Polyethylene Glycol (15)-Hydroxystearate; Polyoxyethylated 12-hydroxystearic Acid; Полиэтиленгликоля 15 Гидроксистеарат.
CAS — 70142-34-6.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Macrogol 15 Hydroxystearate). A mixture of mainly mono- and di-esters of 12-hydroxystearic acid and macrogols obtained by ethoxylation of 12-hydroxystearic acid. The number of moles of ethylene oxide reacted per mole of 12-hydroxystearic acid is 15 (nominal value). It contains free macrogols. A yellowish, waxy mass. It solidifies at about 25 degrees. Very soluble in water; soluble in alcohol; insoluble in liquid paraffin. Store in airtight containers.

USNF 31: (Polyoxyl 15 Hydroxystearate). A product resulting from the reaction of about 15 moles of ethylene oxide with 1 mole of 12-hydroxystearic acid. It consists mainly of 12-hydroxystearic acid polyethoxylated at both the carboxyl and the hydroxyl groups with macrogol. It contains free macrogols. A yellowish to white waxy mass. Very soluble in water; soluble in alcohol and in isopropyl alcohol; insoluble in liquid paraffin. Store in airtight containers at a temperature below 25 degrees, the point at which it solidifies.

Profile

Macrogol 15 hydroxystearate is a macrogol ester nonionic surfactant (p. 2164.2). It is used as a solubilising agent.

Macrogol Laurates

PEG Laurates; Polyethylene Glycol Laurates; Polyoxyl Laurates.
CAS — 9004-81-3.

Profile

Macrogol laurates are macrogol ester nonionic surfactants (p. 2164.2) used as emulsifiers.

Macrogol Lauril Ethers

α-Dodecyl-ω-hydroxypoly(oxyethylene); Éteres laurílicos de macrogol; Laureth Compounds; Lauromacrogols; Macrogol, éteres lauricos de; Macrogol, éther laurique de; Macrogol Lauryl Ethers; Macrogoli aether laurilicum; Makrogolilauryylieetteri; Makrogolio laurilo eteris; Makrogollauryleter; Oxypolyethoxydodecanes; Polyoxyl Lauryl Ethers; Полиэтиленгликоля и Лаурилового Спирта Эфиры.
CAS — 9002-92-0.

Description. Macrogol lauril ethers have the general formula $C_{12}H_{25}(OCH_2CH_2)_nOH$.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Macrogol Lauryl Ether). A mixture of ethers of mixed macrogols with fatty alcohols, mainly $C_{12}H_{26}O$. It contains a variable amount of free $C_{12}H_{26}O$ and it may contain free macrogols. The number of moles of ethylene oxide reacted per mole of $C_{12}H_{26}O$ is 3 to 23 (nominal value). Macrogol lauril ether with 3 to 5 units of ethylene oxide per molecule is a colourless liquid. Practically insoluble in water and in petroleum spirit; soluble or dispersible in alcohol. Macrogol lauril ether with 9 to 23 units of ethylene oxide per molecule is a white or almost white, waxy mass. Soluble or dispersible in water; soluble in alcohol; practically insoluble in petroleum spirit. Macrogol lauril ether should be stored in airtight containers.

USNF 31: (Polyoxyl Lauryl Ether). A mixture of the monolauril ethers of mixed polyethylene glycols, the average polymer length being equivalent to not less than 3 and not more than 23 oxyethylene units (nominal value). It

contains various amounts of free lauril alcohol, and it may contain some free polyethylene glycols. Store in airtight containers in a dry place at a temperature of 8 degrees to 15 degrees.

Laureth 4 *(USAN)*

Лаурет 4.
CAS — 9002-92-0.
UNII — 6HQ855798J.

Description. A mixture of monolauril ethers of macrogols where the average value of *n* in the formula given on p. 2193.3 is 4.

Lauromacrogol 400 *(rINN)*

Laureth 9 (USAN); Lauromacrogolum 400; Polidocanol; Polidocanol 600; Polidocanolum; Polidocanolum 600; Polidokanol; Polidokanoli; Лауромакрогол 400.
CAS — 9002-92-0; 3055-99-0.
ATC — C05BB02.
ATC Vet — QC05BB02.
UNII — 0AWH8BFG9A.

Description. Lauromacrogol 400 is a mixture of monolauril ethers of macrogols where the average value of *n* in the formula given on p. 2193.3 is 9. It has sometimes, however, been erroneously described as containing 8, rather than 9, oxyethylene groups. However, note that Lauromacrogol *(BAN)* is described as containing an average of 8 ethylene oxide groups per molecule.

The number 400 in the name Lauromacrogol 400 corresponds approximately to the average molecular mass of the macrogol portion whereas the number 600 in the name Polidocanol 600 corresponds approximately to the average molecular mass of the whole molecule.

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

Ph. Eur. 8: (Lauromacrogol 400). A mixture of lauril alcohol (dodecanol) monoethers of mixed macrogols. It may contain some free macrogols and it contains various amounts of free lauril alcohol. The number of moles of ethylene oxide reacted per mole of lauril alcohol is 9. The number (400) following the name approximately corresponds to the average molecular mass of the macrogol portion. A white or almost white, unctuous, and hygroscopic mass, which melts at 24 degrees into a colourless or yellowish, viscous liquid. Freely soluble in water; very soluble in alcohol and in acetone.

Uses and Administration

Macrogol lauril ethers are mixtures of macrogol ethers of mainly lauril alcohol. They are macrogol alkyl ether nonionic surfactants (p. 2164.2) and are used as solubilisers and dispersants; they have also been used as spermicides. Lauromacrogol 400 is used as a sclerosant in the treatment of oesophageal and gastric varices (p. 2563.1) and varicose veins (p. 2564.1), and has been tried in endoscopic injection therapy for bleeding peptic ulcer (p. 1813.2); it has also been used as a local anaesthetic and antipruritic (see p. 1687.3) in combination topical preparations.

Adverse Effects

There have been occasional reports of allergic skin reactions after topical application of preparations containing macrogol lauril ethers.

A 63-year-old man developed pulmonary oedema, a dramatic fall in heart rate, transient left pyramidal syndrome and died after sclerotherapy with lauromacrogol 400 to control gastric variceal bleeding:[1] the fatality was attributed to the action of the drug that had passed into the systemic circulation. Another patient[2] suffered a reversible ischaemic neurological deficit after sclerotherapy with lauromacrogol 400 for varicose veins of the leg, and ischaemic stroke[3] and other neurological symptoms,[4] probably due to embolism after passage of foam through a patent foramen ovale, have been reported after foam injection sclerotherapy using the compound. Allergic respiratory symptoms have reported[5] in a patient on the sixth occasion of her receiving lauromacrogol 400 as sclerotherapy for varicose veins; no adverse events had occurred during five previous treatment sessions.

A study[6] involving 1605 patients that covered 3357 patient years revealed 5 adverse events with liquid, and 46 with foam, preparations of lauromacrogol 400. Visual disturbances were the most frequent event (14) and muscular vein thrombosis the most serious (8). Overall, it was considered that lauromacrogol 400 was a safe sclerosing agent for varicose veins.

1. Paterlini A, *et al.* Heart failure and endoscopic sclerotherapy of variceal bleeding. *Lancet* 1984; I: 1241.
2. Van der Plas JPL, *et al.* Reversible ischaemic neurological deficit after sclerotherapy of varicose veins. *Lancet* 1994; 343: 428.
3. Porlee MV, *et al.* Stroke after varicose vein foam injection sclerotherapy. *J Vasc Surg* 2006; 43: 162–4.
4. Ceulen RPM, *et al.* Microembolism during foam sclerotherapy of varicose veins. *N Engl J Med* 2008; 358: 1525–6.
5. Gesilin JM, *et al.* Manifestations respiratoires allergiques lors de sclérose de varices par le lauromacrogol 400. *Therapie* 2004; 59: 651–2.
6. Guex JJ, *et al.* The French polidocanol study on long-term side effects: a survey covering 3,357 patient years. *Dermatol Surg* 2010; 36 (suppl 2): 993–1003.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aet; Aetoxysklerol; *Austral.*: Aethoxysklerol; *Austria*: Aethoxysklerol; *Belg.*: Aethoxysklerol; *Cz.*: Aethoxysklerol; *Denm.*: Aethoxysklerol; *Fin.*: Aethoxysklerol; *Fr.*: Aetoxisclerol; *Ger.*: Aethoxysklerol; Anaesthesulf; Pruriderm; Recessan; *Gr.*: Aethoxysklerol; Atossisclerol; Etoxisklerol; *Hung.*: Aethoxysklerol; *India*: Asklerol; *Israel*: Polidoc†; *Ital.*: Atossisclerol; *Mex.*: Farmaflebon; *Neth.*: Aethoxysklerol; *Pol.*: Aethoxysklerol; *Spain*: Etoxisclerol; *Swed.*: Aethoxysklerol; *Switz.*: Aethoxysklerol; Balmed Hermal Plus; Sclerovein; *Thai.*: Aethoxysklerol; *Turk.*: Aethoxysklerol; *Ukr.*: Sclerovein (Склеровейн); *USA*: Asclera; Varithena; *Venez.*: Etoxisclerol.

Multi-ingredient Preparations. *Arg.*: Nene Dent NF; *Austria*: Balneum Plus; Dentinox†; Dentinox; Optiderm; Prurimix; Solcoseryl Dental; Vonum; *Belg.*: Cose-Anal; *Braz.*: Nene Dent N; *Chile*: Mentobalsam†; Ureadin Rx DB; Ureadin Rx PS; Ureadin Rx RD; Vatanal; *Cz.*: Balneum Hermal Plus; *Ger.*: Balneum Plus; Brand- u. Wundgel-Medice; Dentinox N; Optiderm; Solcoseryl akut†; Solcoseryl Dental†; *Hong Kong*: Collomack†; Haemoral†; Solcoseryl Dental; *Hung.*: Balneum Hermal Plus; Dentinox N; Dentinox; *Indon.*: Solcoseryl Dental†; *Irl.*: Balneum Plus†; Itch Relief; *Israel*: Balneum Plus; Derma-Care†; *Ital.*: Optiderm; Pitiren; *Malaysia*: Balneum Intensiv Plus; Solcoseryl Dental; *Mex.*: Nene Dent; *Neth.*: Epianal; *Norw.*: Alcos-Anal; *Philipp.*: Solcoseryl Dental; *Pol.*: Balneum Hermal Plus†; Dentinox N; Optiderm†; *Port.*: Anacal; Hidratante VV; *Rus.*: Collomac (Колломак); Dentinox (Дентинокс); Hepatrombin H (Гепатромбин Г); Solcoseryl Dental (Солкосерил Дентальная); *Singapore*: Balneum Intensiv Plus; Solcoseryl Dental; *Switz.*: Assan rem; Decasept N†; Dentinox; Optiderm; Oxydermine; Parapic Pruri-med Lipolotion; Pruri-med; Solcoseryl Dentaire; Sportusal Spray sine heparino; Sportusal; Venucreme; Venugel; *Thai.*: Collomak; Solcoseryl Dental; *Turk.*: Dentinox; Kortos; Solcoseryl; *UK*: Anacal; Balneum Plus; Balneum Plus; Diprobath†; E45 Itch Relief; *Ukr.*: Collomak (Колломак); Dentinox N (Дентинокс Н); Hepathrombin H (Гепатромбин Г); Solcoseryl Dental (Солкосерил Дентальная); *Venez.*: Collomack.

Macrogol Monomethyl Ethers

Éteres monometílicos de polietilenglicol; Macrogol, éteres monometílicos de; Methoxy-PEGs; Methoxypolyethylene Glycols; MPEGs; Polyethylene Glycol Monomethyl Ethers; Polyoxyethylene Monomethyl Ethers; Полиэтиленгликоля и Метилового Спирта Эфиры.
α-Methyl-ω-hydroxypoly(oxyethylene).
CAS — 9004-74-4.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyethylene Glycol Monomethyl Ether). Addition polymers of ethylene oxide and methyl alcohol, represented by the formula $CH_3(OCH_2CH_2)_nOH$, where *n* represents the average number of oxyethylene groups. The name is usually designated by a number that corresponds approximately to its average molecular weight.

As the average molecular weight increases, the water solubility, vapour pressure, hygroscopicity, and solubility in organic solvents decrease while congealing temperature, specific gravity, flash-point, and viscosity increase. Liquid grades occur as clear to slightly hazy, colourless or practically colourless, slightly hygroscopic, viscous liquids with a slight characteristic odour. Solid grades occur as practically odourless, white, waxy, plastic material with a consistency similar to beeswax, or as creamy white flakes, beads, or powders. Liquid grades are miscible with water; solid grades are freely soluble in water; all grades are soluble in alcohol, in acetone, in chloroform, in ethyl acetate, in ethylene glycol monoethyl ether, and in toluene; all grades are insoluble in ether and in hexane. Store in airtight containers.

Profile

Macrogol monomethyl ethers are macrogol ether nonionic surfactants (p. 2164.2). They may be used as ointment bases, solvents, and plasticisers.

Macrogol Oleates

Macrogol Mono-oleates; Macrogol, oléate de; Macrogoli Oleas; Makrogolio oleatas; Makrogolioleaatti; Makrogololeat; Makrogol-oleát; Polyethylene Glycol Monooleates; Polyoxyl Oleates.
CAS — 9004-96-0.

Pharmacopoeias. *Eur.* (see p. vii) includes a monograph for Macrogol Oleate. *USNF* includes Polyoxyl Oleate.

Ph. Eur. 8: (Macrogol Oleate). A mixture of mono- and di-esters of mainly oleic (cis-9-octadecenoic) acid and macrogols. It may be obtained by ethoxylation of oleic acid or by esterification of macrogols with oleic acid of animal or vegetable origin. It may contain free macrogols. The average polymer length is equivalent to 5 to 6 or 10 moles of ethylene oxide per mole (nominal value). A suitable antoxidant may be added. A slightly yellowish, viscous liquid. Dispersible in water and in oils; soluble in alcohol and in isopropyl alcohol; miscible with fatty oils and with waxes. It has a refractive index of about 1.466. Store in airtight containers.

USNF 31: (Polyoxyl Oleate). A mixture of the mono- and di-esters of oleic acid and mixed polyethylene glycols. It may be obtained by ethoxylation of oleic acid or by esterification of polyethylene glycols with oleic acid of animal or vegetable origin. It may contain free polyethylene glycol. The average polymer length is equivalent to either 5 to 6 or 10 oxyethylene units (nominal values). A suitable antoxidant may be added. A slightly yellowish, viscous liquid. Dispersible in water and in oils; soluble in alcohol and in isopropyl alcohol; miscible with fatty oils and with waxes. Its refractive index is about 1.466. Store in airtight containers. Protect from moisture.

Profile

Macrogol oleates are macrogol ester nonionic surfactants (p. 2164.2) used as emulsifiers.

Macrogol Oleyl Ethers

Ethoxylated Oleyl Alcohol; Macrogol, éteres oleílicos de; Macrogol, éther oléique de; Macrogoli aether oleicum; Macrogoli Aetherum Oleicum; Makrogolio oleilo eteris; Makrogolioleyylieetteri; Makrogol-oleil-éter; Makrogololeyleter; Oleth Compounds; Polyethylene Glycol Mono-oleyl Ethers; Полиэтиленгликоля и Олеилового Спирта Эфиры.
CAS — 9004-98-2.

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

Ph. Eur. 8: (Macrogol Oleyl Ether). A mixture of ethers of mixed macrogols with linear fatty alcohols, mainly oleyl alcohol. It may contain some free macrogols and it contains various amounts of free oleyl alcohol. Macrogol oleyl ether with 2 to 5 units of ethylene oxide per molecule is a yellow liquid. Practically insoluble in water and in petroleum spirit; soluble in alcohol. Macrogol oleyl ether with 10 to 20 units of ethylene oxide per molecule is a yellowish-white, waxy mass. Dispersible or soluble in water; soluble in alcohol; practically insoluble in petroleum spirit. Macrogol oleyl ethers should be stored in airtight containers. Protect from light.

Polyoxyl 10 Oleyl Ether

Polioxil 10, éter oleílico de; Полиоксиэтиленгликоля и Олеиновой Кислоты Эфир.
UNII — JD797EF70J.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyoxyl 10 Oleyl Ether). A mixture of the mono-oleyl ethers of mixed macrogols, the average polymer length being equivalent to not less than 9.1 and not more than 10.9 oxyethylene units. It may contain suitable stabilisers.

A soft white semisolid or pale yellow liquid with a bland odour. Soluble in water and in alcohol; dispersible in liquid paraffin and in propylene glycol with possible separation on standing. Store at a temperature of 8 degrees to 15 degrees in airtight containers.

Profile

Macrogol oleyl ethers are mixtures of macrogol ethers of mainly oleyl alcohol. They are macrogol ether nonionic surfactants (p. 2164.2) and are used as emulsifying and solubilising agents.

Macrogol Poly(vinyl Alcohol) Grafted Copolymer

Ethenol Graft Polymer with Oxirane; Ethylene Glycol and Vinyl Alcohol Graft Copolymer; Macrogol-Poly(vinylalkohol)-

Привитой сополимер Поливинилового Спирта и Полиэтиленгликоля; Polyvinyl Alcohol-Polyethylene Glycol Graft Copolymer; PVA-PEG Graft Copolymer.
CAS — 96734-39-3; 121786-16-1.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Macrogol Poly(vinyl Alcohol) Grafted Copolymer); Copolymerum Macrogolo et Alcoholi Poly (vinylico) Constatum. A grafted copolymer of macrogol and poly(vinyl alcohol), having a mean relative molecular mass of about 45 000. It consists of about 75% of poly(vinyl alcohol) units and 25% of macrogol units. It may contain anhydrous colloidal silica to improve flowability. A white or slightly yellowish powder; opalescent solutions may be obtained during testing due to the presence of anhydrous colloidal silica. Very soluble in water; practically insoluble in dehydrated alcohol and in acetone. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 20% solution in water has a pH of 5.0 to 8.0.

USNF 31: (Ethylene Glycol and Vinyl Alcohol Graft Copolymer). A graft copolymer of ethylene glycol and vinyl alcohol. It consists of about 75% of vinyl alcohol units and 25% of ethylene glycol units. The copolymer is produced by using macrogol and vinyl acetate as starting materials. The macrogol forms the polymer backbone onto which polyvinyl acetate is grafted. Hydrolysis of polyvinyl acetate side-chains leads to formation of polyvinyl alcohol grafted chains. It may contain a glidant to improve flowability. A white or slightly yellowish powder. Very soluble in water; practically insoluble in anhydrous alcohol and in acetone. It dissolves in dilute acids and dilute solutions of alkali hydroxides. A 20% solution in carbon dioxide-free water has a pH of 5.0 to 8.0. Store at a temperature below 25 degrees.

Profile

Macrogol poly(vinyl alcohol) grafted copolymer is used in film coatings for immediate-release tablets and pellets.

Macrogol 40 Sorbitol Heptaoleate

Macrogol 40 Sorbitoli Heptaoleas; Macrogol-40-sorbitolheptaoleat.

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

Ph. Eur. 8: (Macrogol 40 Sorbitol Heptaoleate). A mixture of esters of fatty acids, mainly oleic acid, and sorbitol ethoxylated with approximately 40 moles of ethylene oxide for each mole of sorbitol. 7 moles of oleic acid are used for each mole of sorbitol. It also contains macrogol fatty acid esters. A clear or slightly opalescent, yellowish, viscous, hygroscopic liquid. Dispersible in water; soluble in isopropyl myristate, in isopropyl palmitate, in mineral oils, and in vegetable fatty oils. Store in airtight containers. Protect from light.

Profile

Macrogol 40 sorbitol heptaoleate is a macrogol sorbitol ester, similar to the polysorbates but containing about 40 moles of ethylene oxide per mole of sorbitol rather than 20. It is a sorbitan ester nonionic surfactant (p. 2164.2) and is used as an emulsifier in topical preparations.

Macrogol Stearates

Ésteres de polietilenglicol; Ésteres de polioxietileno; Macrogol, ésteres del; Macrogol, stéarate de; Macrogoli Stearas; Makrogolio stearatas; Makrogolistearaatti; Makrogolstearat; Makrogol-stearát; Makrogol-sztearát; Polyoxyethylene Glycol Stearates; Polyoxyethylene Stearates; Polyoxyl Stearates; Макрогола Стеараты; Полиэтиленгликоля Стеараты.
CAS — 9004-99-3.

Nomenclature. There are two systems of nomenclature used for these compounds; these substances have the general formula $C_{17}H_{35}COO.[O.CH_2CH_2]_n.H$. In the systems used by *BAN* and *USAN* the numbers in the names refer to the approximate polymer length in oxyethylene units whereas in the system used by *INN* the number refers to the average molecular weight of the polymer chain. Thus, the names Macrogol 8 Stearate (*BAN*), Polyoxyl 8 Stearate (*USAN*), and Macrogol Stearate 400 (*rINNM*) all describe the same compound.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Macrogol Stearate). A mixture of the mono- and di-esters of mainly stearic acid and/or palmitic acid and macrogols. It may be obtained by ethoxylation or by esterification of macrogols with stearic acid 50 (type I) or stearic acid 95 (type II). The average polymer length is equivalent to 6 to 100 ethylene oxide units per molecule (nominal value). It may contain free macrogols. White or slightly yellowish waxy mass. Soluble in alcohol and in isopropyl alcohol. Compounds containing 6 to 9 units of ethylene oxide per molecule are practically insoluble but freely dispersible in water; miscible with fatty oils and with waxes. Compounds containing 20 to 100 units of ethylene oxide per molecule are soluble in water; practically insoluble in fatty oils and in waxes. Store in airtight containers.

USNF 31: (Polyoxyl Stearate). A mixture of the mono- and di-esters of mainly stearic (octadecanoic) acid and/or palmitic (hexadecanoic) acid and polyethylene glycols. The fatty acids may be of vegetable, animal, or synthetic origin. Polyoxyl Stearate Type I or Type II differs in its content of stearic acid. It may contain free polyethylene glycols. The average polymer length is equivalent to 6 to 100 ethylene oxide units per molecule (nominal value). A white or slightly yellowish waxy mass. Soluble in alcohol and in isopropyl alcohol. Polyoxyl stearate corresponding to a product with 6 to 8 units of ethylene oxide per molecule is practically insoluble in water; soluble in fatty oils and in waxes. Polyoxyl stearate corresponding to a product with 20 to 100 units of ethylene oxide per molecule is soluble in water; practically insoluble in fatty oils and in waxes.

Store in airtight containers. Protect from light and moisture.

Polyoxyl 40 Stearate *(USAN)*

E431; Estearato de macrogol 2000; Estearato de Polioxila 40; Macrogol 2000, Stéarate de; Macrogol 40 Stearate (BAN); Macrogol Ester 2000; Macrogol Stearate 2000 (rINNM); Macrogol Stearate 2000; Macrogoli Stearas 2000; Polyoxyethylene 40 Stearate; Stearethate 40; Макрогола 2000 Стеарат.
UNII — 13A4J4NH9I (polyoxyl stearate); ECU18C66Q7 (polyoxyl 40 monostearate); 1PC44PS35Z (polyoxyl 40 distearate).

Pharmacopoeias. In *Jpn.* Also in *USNF.*

USNF 31: (Polyoxyl 40 Stearate). A mixture of the mono- and di-esters of stearic acid and mixed macrogols, the average polymer length being about 40 oxyethylene units. It contains not less than 17% and not more than 27% of free macrogols. It is a waxy, white to light tan solid, odourless or with a faint fat-like odour. Congealing range 37 degrees to 47 degrees. Soluble in water, in alcohol, in acetone, and in ether; insoluble in liquid paraffin and in vegetable oils. Store in airtight containers.

Incompatibility. Macrogol stearates have been reported to be generally stable with electrolytes and weak acids or bases although strong acids or bases may cause hydrolysis and saponification. Discoloration or precipitation may occur with phenolic substances and complexation with preservatives. Decrease in the antimicrobial activity of bacitracin, chloramphenicol, phenoxymethylpenicillin, and tetracycline has been stated to occur with concentrations of macrogol stearates exceeding 5%.

Profile

Macrogol stearates are macrogol ester nonionic surfactants (p. 2164.2) that are used as emulsifying and solubilising agents.

Macrogolglycerol Cocoates

Macrogol Glycerol Cocoates; Macrogol Glyceryl Cocoates; Macrogolglycerolcocoate; Macrogolglyceroli Cocoates; PEG Glyceryl Cocoates; Polyethylene Glycol Glyceryl Cocoates.

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

Ph. Eur. 8: (Macrogolglycerol Cocoates). Mixtures of mono-, di-, and triesters of ethoxylated glycerol with fatty acids of vegetable origin having a composition corresponding to the fatty acid composition of the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera*. The average number of moles of ethylene oxide reacted per mole of substance (nominal value) is either 7 (macrogol 7 glycerol cocoate) or 23 (macrogol 23 glycerol cocoate). Relative density about 1.05 for macrogol 7 glycerol cocoate and about 1.09 for macrogol 23 glycerol cocoate A clear, yellowish, oily liquid. Soluble in water and in alcohol; practically insoluble in petroleum spirit at 50 degrees to 70 degrees for macrogol 7 glycerol cocoate and macrogol 23 glycerol cocoate.

Profile

Macrogolglycerol cocoates are ethoxylated glycerol ester nonionic surfactants (p. 2164.2). They are used as nonionic surfactants cleansers, emulsifiers and solubilisers in topical preparations.

Magnesium Silicate

E553(a); Silicato de magnesio; Магний Кремнекислый; Силикат Магния.
CAS — 1343-88-0.
ATC — A02AA05.
ATC Vet — QA02AA05.
UNII — 9B9691B2N9.

NOTE. The code E553(a) has also been applied to magnesium trisilicate.

Pharmacopoeias. In *Jpn.* Also in *USNF.*

USNF 31: (Magnesium Silicate). A compound of magnesium oxide and silicon dioxide. It contains not less than 15.0% of magnesium oxide and not less than 67.0% of silicon dioxide, calculated on the ignited basis. It is a fine, white, odourless powder, free from grittiness. Insoluble in water and in alcohol. It is readily decomposed by mineral acids. pH of a well-mixed 10% suspension in water is between 7.0 and 10.8.

Profile

Magnesium silicate is used in the food industry and in pharmaceutical manufacturing as an anticaking agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Port.*: Acnoil Free†.

Multi-ingredient Preparations. *Braz.*: Cutisanol; *Fr.*: ZeaSorb.

Magnesium Stearate

572; E470b (magnesium salts of fatty acids); Estearato de magnesio; Estearato de Magnésio; Magnesii Stearas; Magnésium, stéarate de; Magnesiumstearaat; Magnesiumstearaatti; Magnesiumstearat; Magnézium-sztearát; Magnezu stearynian; Magnio stearatas; Stearan hořečnatý; Stéarate de magnésium; Stearato di magnesio; Stearynian magnezu; Стеарат Магния.
Magnesium octadecanoate.
CAS — 1555-53-9 (magnesium oleate); 2601-98-1 (magnesium palmitate); 557-04-0 (magnesium stearate).
UNII — 70097M6I30.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.* Also in *USNF.*

Ph. Eur. 8: (Magnesium Stearate). A compound of magnesium with a mixture of solid organic acids and consisting mainly of variable proportions of magnesium stearate ($C_{36}H_{70}MgO_4$ = 591.3) and magnesium palmitate ($C_{32}H_{62}MgO_4$ = 535.1) obtained from sources of vegetable or animal origin. It contains 4.0 to 5.0% of magnesium calculated on the dried substance. The fatty acid fraction contains not less than 40.0% of stearic acid and the sum of stearic acid and palmitic acid is not less than 90.0%. A white or almost white, very fine, light powder, greasy to the touch. Practically insoluble in water and in dehydrated alcohol.

USNF 31: (Magnesium Stearate). A compound of magnesium with a mixture of solid organic acids, and consisting mainly of variable proportions of magnesium stearate ($C_{36}H_{70}MgO_4$ = 591.3) and magnesium palmitate ($C_{32}H_{62}MgO_4$ = 535.1). It is a very fine, light, white powder, slippery to touch. Insoluble in water, in alcohol, and in ether.

Profile

Magnesium stearate is a metal soap anionic surfactant (p. 2164.1). It is used as a lubricant in the manufacture of tablets and capsules, and has been used as a dusting powder and in barrier creams. It is also used in foods, cosmetics, and other industrial applications.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Holomagnesio Vital; *Israel*: Acti Talc; *Ital.*: Ferromina; *Philipp.*: Exofat; Johnson's Baby Double Protection Powder; Thinber Fiber Complex†; *UK*: Calci-Plus.

Homoeopathic Preparations. *Canad.*: Biomag†.

Maleic Acid

Acide maléique; Ácido cis-buteno dioico; Acido Maleico; Ácido maleínico; Acidum Maleicum; (Z)-Butenedioic Acid; Kwas maleinowy; Kyselina maleinová; Maleico, ácido; Maleiinihappo; Maleïnezuur; Maleino rūgštis; Maleinsäure; Maleinsav; Maleinsyra; Maleinskābe; Toxilic Acid; Малеиновая Кислота.

The symbol † denotes a preparation no longer actively marketed

cis-Butenedioic acid.
$C_2H_2(CO_2H)_2$=116.1
CAS — 110-16-7.
UNII — 91XW058U2C.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Maleic Acid). A white or almost white, crystalline powder. Freely soluble in water and in alcohol. A 5% solution in water has a pH of less than 2. Store in glass containers. Protect from light.

USNF 31: (Maleic Acid). A white crystalline powder. Freely soluble in water and in alcohol; sparingly soluble in ether. Store in airtight glass containers. Protect from light.

Profile

Maleic acid is a dicarboxylic acid used to adjust the acidity of pharmaceutical preparations and as an acidulant in foods.

Maltol

636; Мальтол.
3-Hydroxy-2-methyl-4-pyrone.
$C_6H_6O_3$=126.1
CAS — 118-71-8.
UNII — 3A9RD92BS4.

Pharmacopoeias. In *USNF.*

USNF 31: (Maltol). A white, crystalline powder having a characteristic caramel-butterscotch odour, suggestive of a fruity-strawberry aroma in dilute solution. 1 g dissolves in about 82 mL of water, in 21 mL of alcohol, in 80 mL of glycerol, and in 28 mL of propylene glycol. Store in airtight container. Protect from light.

Ethyl Maltol

637; Этил Мальтол.
2-Ethyl-3-hydroxy-4-pyrone.
$C_7H_8O_3$=140.1
CAS — 4940-11-8.
UNII — L6Q8K29L05.

Pharmacopoeias. In *USNF.*

USNF 31: (Ethyl Maltol). A white, crystalline powder having a cotton-candy odour and a sweet, fruitlike flavour in dilute solution. One g dissolves in about 55 mL of water, 10 mL of alcohol, 17 mL of propylene glycol, and 5 mL of chloroform. Store in airtight containers.

Profile

Maltol is used as a flavouring in pharmaceutical formulations and as a food additive. Ethyl maltol is used similarly.

2-Methoxyethanol

Éter monometílico de etilenglicol; Eter monometylowy glikolu etylenowego; Ethylene Glycol Monomethyl Ether; Metilglicol; 2-Metoxietanol; 2-Метоксиэтанол.
$C_3H_8O_2$=76.10
CAS — 109-86-4.
UNII — EK1L6XW156.

Description. 2-Methoxyethanol is a clear, colourless to slightly yellow liquid. Wt per mL about 0.96 g. B.p. about 125 degrees. Miscible with water, with alcohol, with acetone, with dimethylformamide, with ether, and with glycerol. Store in airtight containers.

Uses

2-Methoxyethanol is used as an industrial solvent. Other glycol ethers, such as 2-butoxyethanol (p. 2172.1) and 1-*tert*-butoxy-2-propanol are also used.

Adverse Effects and Precautions

2-Methoxyethanol is irritant to mucous membranes. Ingestion may result in CNS depression with confusion, weakness, and in severe cases coma and death from respiratory depression. Nausea, metabolic acidosis, and renal damage may also occur. Prolonged industrial exposure to the vapour has been associated with severe effects on the CNS characterised by headache, dizziness, lethargy, weakness, ataxia, tremor, disorientation, mental changes, weight loss, and visual disturbances. Anaemia has also been reported. There has been concern about the potential for reproductive toxicity.

References to the toxicity of 2-methoxyethanol and other glycol ethers.

1. Health and Safety Executive. Glycol ethers. *Toxicity Review 10.* London: HMSO, 1985.
2. WHO. 2-Methoxyethanol, 2-ethoxyethanol, and their acetates. *Environmental Health Criteria 115.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc115.htm (accessed 30/06/04)
3. Browning RG, Curry SC. Clinical toxicology of ethylene glycol monoalkyl ethers. *Hum Exp Toxicol* 1994; 13: 325–35.
4. Johanson G. Toxicity review of ethylene glycol monomethyl ether and its acetate ester. *Crit Rev Toxicol* 2000; 30: 307–45.
5. Bagchi G, Waxman DJ. Toxicity of ethylene glycol monomethyl ether: impact on testicular gene expression. *Int J Androl* 2008; 31: 269–74.

Handling. Suitable precautions should be taken to avoid skin contact with 2-methoxyethanol as it can penetrate skin and produce systemic toxicity.

Methyl Alcohol

Alcohol de la madera; Alcohol de quemar; Alcohol metílico; Alkohol metylowy; Brandalcohol; Carbinol; Metanol; Metanoli; Metanolis; Metanolo; Metanols; Metanool; Methanol; Méthanol; Methanolum; Monohidroximetano; Метиловый Спирт; Метанол.
CH_3OH=32.04
CAS — 67-56-1.
UNII — Y4S76JWI15.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Methanol). A colourless, clear, volatile, hygroscopic liquid. It is flammable. B.p. about 64 degrees. Relative density 0.791 to 0.793. Miscible with water and with dichloromethane. Store in airtight containers.

The **BP 2014** gives Methyl Alcohol as an approved synonym.

USNF 31: (Methyl Alcohol). A clear, colourless, flammable liquid having a characteristic odour. Miscible with water, with alcohol, with ether, with benzene, and with most other organic solvents. Store in airtight containers remote from heat, sparks, and open flames.

Uses

Methyl alcohol is used as a pharmaceutical and industrial solvent. It is also used as 'wood naphtha' to denature ethanol in the preparation of industrial methylated spirits. Methyl alcohol is also used as an extraction solvent in food processing.

Adverse Effects

Immediate signs of acute poisoning after ingestion of methyl alcohol resemble those of ethanol (alcohol; ethyl alcohol) intoxication (see p. 1733.3), but are milder. Characteristic symptoms of methyl alcohol poisoning are caused by toxic metabolites and develop after a latent period of about 12 to 24 hours, or longer if taken with ethanol. The outstanding features of poisoning are metabolic acidosis with rapid, shallow breathing, visual disturbances which often proceed to irreversible blindness, and severe abdominal pain. Other symptoms include headache, gastrointestinal disturbances, pain in the back and extremities, and coma which in severe cases may result in death due to respiratory failure or, rarely, to circulatory collapse. Mania and convulsions occasionally occur. Individual response to methyl alcohol varies widely. Ingestion of 30 mL is considered to be potentially fatal.

Absorption of methyl alcohol through the skin or inhalation of the vapour may also lead to toxic systemic effects.

References to the adverse effects of methyl alcohol.

1. Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings: mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol* 1986; 1: 309–34.
2. Anderson TJ, *et al.* Neurologic sequelae of methanol poisoning. *Can Med Assoc J* 1987; 136: 1177–9.
3. Cavalli A, *et al.* Severe reversible cardiac failure associated with methanol intoxication. *Postgrad Med J* 1987; 63: 867–8.
4. Shapiro L, *et al.* Unusual case of methanol poisoning. *Lancet* 1993; 341: 112.
5. Medinsky MA, Dorman DC. Recent developments in methanol toxicity. *Toxicol Lett* 1995; 82–83: 707–11.
6. McKellar MJ, *et al.* Acute ocular methanol toxicity: clinical and electrophysiological features. *Aust N Z J Ophthalmol* 1997; 25: 225–30.
7. Williams GF, *et al.* Methanol poisoning: a review and case study of four patients from central Australia. *Aust Crit Care* 1997; 10: 113–18.
8. Shelby M, *et al.* NTP-CERHR expert panel report on the reproductive and developmental toxicity of methanol. *Reprod Toxicol* 2004; 18: 303–90.
9. Hantson PE. Intoxication aiguë par le méthanol: physiopathologie, pronostic et traitement. *Bull Mem Acad R Med Belg* 2006; 161: 425–34.
10. Paasma R, *et al.* Methanol poisoning and long term sequelae—a six years' follow-up after a large methanol outbreak. *BMC Clin Pharmacol* 2009; 9: 5. Available at: http://www.biomedcentral.com/content/pdf/1472-6904-9-5.pdf (accessed 16/06/10)
11. Jammalamadaka D, Raissi S. Ethylene glycol, methanol and isopropyl alcohol intoxication. *Am J Med Sci* 2010; 339: 276–81.
12. Epker JL, Bakker J. Accidental methanol ingestion: case report. *BMC Emerg Med* 2010; 10: 3. Available at: http://www.biomedcentral.com/content/pdf/1471-227X-10-3.pdf (accessed 27/06/11)
13. Singh A, *et al.* Portrait of a methanol-intoxicated brain. *Am J Med* 2011; 124: 125–7.

Handling. Suitable precautions should be taken to avoid skin contact with methyl alcohol as it can penetrate skin and produce systemic toxicity.

Treatment of Adverse Effects

Gastric aspiration may be considered if the patient presents within 1 hour of ingesting methyl alcohol. Activated charcoal is probably of little use as it does not absorb significant amounts of methyl alcohol. Metabolic acidosis (p. 1775.2) should be corrected immediately with intravenous sodium bicarbonate. If significant amounts of methyl alcohol have been ingested, early treatment with an antidote (ethanol or fomepizole) is recommended. Ethanol delays the oxidation of methyl alcohol to its toxic metabolites formaldehyde and formic acid; dosage is adjusted to achieve and maintain a blood-ethanol concentration of 1 to 1.5 mg/mL. In the UK, the National Poisons Information Service recommends that it be given as follows. An *oral* **loading** dose should be given equivalent to 800 mg/kg of absolute (100% v/v) C_2H_5OH. This may be given in the form of alcoholic spirits such as whisky, gin, or vodka (about 40% v/v C_2H_5OH) in a dose of 2.5 mL/kg. Alternatively, an *intravenous* loading dose of 10 mL/kg of C_2H_5OH 10% v/v may be given over 30 minutes via a central line. Loading doses may be followed by oral or intravenous **maintenance** doses as follows:

orally (as a 40% v/v solution of C_2H_5OH):
- for an average adult, 0.375 mL/kg per hour
- for a non-drinker or child, 0.25 mL/kg per hour
- for a chronic drinker, 0.58 mL/kg per hour

by *intravenous infusion* (as a 10% v/v solution of C_2H_5OH):
- for an average adult, 1.5 mL/kg per hour
- for a non-drinker or child, 1 mL/kg per hour
- for a chronic drinker, 2.3 mL/kg per hour

A 5% v/v solution of C_2H_5OH may be given either *orally* or *intravenously* at twice the maintenance doses described above for the 10% solution.

Maintenance doses should be continued until methyl alcohol concentrations are undetectable, or have fallen below 50 micrograms/mL with resolution of systemic toxicity.

Fomepizole (p. 1553.1), an inhibitor of alcohol dehydrogenase, is also used; it inhibits the metabolism of methyl alcohol to its toxic metabolites.

Haemodialysis may be indicated to increase the removal of methyl alcohol and its toxic metabolites. Peritoneal dialysis has been used but is less efficient. Haemodialysis may be considered if the blood-methyl alcohol concentration is greater than 500 micrograms/mL, if there is severe metabolic acidosis unresponsive to sodium bicarbonate, or there is visual disturbance, CNS toxicity, renal failure, or severe electrolyte disturbance. If haemodialysis is used, a constant blood-ethanol concentration may be ensured either by increasing the ethanol infusion rate or by addition of ethanol to the dialysate fluid.

Treatment should not be stopped prematurely since oxidation and excretion of methyl alcohol may continue for several days; patients should, therefore, be closely observed and monitored. Suitable supportive treatment should be carried out as required.

Folinic acid and folic acid have been given in the treatment of methyl alcohol toxicity because they may enhance the metabolism of formic acid.

References.

1. Barceloux DG, *et al.* American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol* 2002; 40: 415–46.

Pharmacokinetics

Methyl alcohol is readily absorbed from the gastrointestinal tract and distributed throughout the body fluids. It may also be absorbed after inhalation or through large areas of skin. Oxidation by alcohol dehydrogenase with formation of formaldehyde and formic acid takes place mainly in the liver and also in the kidneys. These metabolites are thought to be largely responsible for the characteristic symptoms of methyl alcohol poisoning. Metabolism is much slower than for ethanol, which competitively inhibits the metabolism of methyl alcohol. Oxidation and excretion may continue for several days after ingestion. Elimination of unchanged methyl alcohol via the lungs and in the urine is a minor route of excretion.

References.

1. Coulter CV, *et al.* The pharmacokinetics of methanol in the presence of ethanol: a case study. *Clin Pharmacokinet* 2011; 50: 245–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India:* Methazil†.

Methyl *tert*-Butyl Ether

Éter metil *terc*-butílico; Éter metilterbutílico; Eter *tert*-butylowo-metylowy; Methyl Terbutyl Ether; Methyl tert-butyl ether; Methyl Tertiary Butyl Ether; Metil-t-butil eetere;

Metüültert-butüüleeter; Metyylitertiääributyylieetteri; MTBE; tert-Butylmethylether; Метил-трет-бутиловый Эфир.
2-Methoxy-2-methylpropane.
$C_5H_{12}O$=88.15
CAS — 1634-04-4.
UNII — 29I4YB3S89.

Description. Methyl *tert*-butyl ether is a volatile, flammable liquid. Wt per mL about 0.74 g. B.p. about 55 degrees. Store in airtight containers.

Stability. Explosive peroxides may be generated by the atmospheric oxidation of methyl *tert*-butyl ether, but the risk is lower than with solvent ether.

Uses and Administration

Methyl *tert*-butyl ether is used as an industrial solvent. It has also been used for the dissolution of cholesterol gallstones, but is no longer generally recommended (see below).

Gallstones. Gallstones (p. 2639.1) are usually treated surgically, but therapy with oral bile acids to dissolve the stones may have a role in some patients. Direct instillation of solvents into the gallbladder has also been tried, and positive results have been reported[1-4] with use of methyl *tert*-butyl ether. However, the technique is not generally recommended due to the frequency and severity of complications. Nausea has been reported in about one-third of patients, sometimes with vomiting, and sedation may also occur. Severe complications that have been reported include ulcerative duodenitis and intravascular haemolysis,[1] and coma and acute renal failure.[5]

1. Thistle JL, *et al.* Dissolution of cholesterol gallbladder stones by methyl *tert*-butyl ether administered by percutaneous transhepatic catheter. *N Engl J Med* 1989; 320: 633–9.
2. Foerster E-Ch, *et al.* Direct dissolution of gallbladder stones. *Lancet* 1989; i: 954.
3. Hellstern A, *et al.* Gall stone dissolution with methyl tert-butyl ether: how to avoid complications. *Gut* 1990; 31: 922–5.
4. McNulty J, *et al.* Dissolution of cholesterol gall stones using methyltertbutyl ether: a safe effective treatment. *Gut* 1991; 32: 1550–3.
5. Ponchon T, *et al.* Renal failure during dissolution of gallstones by methyl-*tert*-butyl ether. *Lancet* 1988; ii: 276–7.

Adverse Effects

Methyl *tert*-butyl ether is irritant and may cause CNS depression. Adverse effects that have been reported after use as a gallstone solvent are described under Uses and Administration, above.

Methyl Butyl Ketone

Butilmetilcetona; 2-Hexanone; MBK; Methyl *n*-Butyl Ketone; Metil-*n*-butilcetona; Metilbutilcetona; Propylacetone; Метил-бутилкетон.
Hexan-2-one.
$C_6H_{12}O$=100.2
CAS — 591-78-6.
UNII — 6GDY60NH6N.

Description. Methyl butyl ketone is a colourless, volatile liquid. Wt per mL about 0.82 g. B.p. about 127 degrees. Store in airtight containers.

Methyl Isobutyl Ketone

Hexone; Isobutilmetilcetona; Isopropylacetone; Méthylisobutylcétone; Methylisobutylketon; Metilisobutilchetone; Metyyli-isobutyyliketoni; MIBK; Метилизобутилкетон.
4-Methylpentan-2-one.
$C_6H_{12}O$=100.2
CAS — 108-10-1.
UNII — U5T7B88CNP.

Pharmacopoeias. In *USNF.*

USNF 31: (Methyl Isobutyl Ketone). A transparent, colourless, mobile, volatile liquid having a faint ketonic and camphoraceous odour. Sp. gr. not more than 0.799. Distilling range 114 degrees to 117 degrees. Slightly soluble in water; miscible with alcohol, with ether, and with benzene. Store in airtight containers.

Uses

Methyl isobutyl ketone is used as an industrial and pharmaceutical solvent and also as an alcohol denaturant. Methyl butyl ketone is used as an industrial solvent.

Adverse Effects and Precautions

Methyl butyl ketone and methyl isobutyl ketone may depress the CNS in high concentrations. Their vapours are irritating to mucous membranes. Methyl isobutyl ketone may be implicated in volatile substance abuse (see under Toluene, p. 2216.3).

References.
1. WHO. Methyl isobutyl ketone. *Environmental Health Criteria 117.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc117.htm (accessed 30/06/04)
2. WHO. Methyl isobutyl ketone health and safety guide. *IPCS Health and Safety Guide 58.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg058.htm (accessed 30/06/04)

Effects on the nervous system. Peripheral neuropathy[1] has occurred after occupational exposure to methyl butyl ketone, particularly an outbreak of neuropathy in a printing plant after the replacement of methyl isobutyl ketone by methyl butyl ketone in a solvent mixture with methyl ethyl ketone. Methyl ethyl ketone may have potentiated the neurotoxicity induced by methyl butyl ketone.

For further discussion of neurotoxicity after occupational exposure to solvents including methyl butyl ketone, see under Toluene, p. 2216.2.

1. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; 8: 293–300.

Handling. Suitable precautions should be taken to avoid skin contact with methyl butyl ketone or methyl isobutyl ketone as they can penetrate skin and produce systemic toxicity.

Methyl Chloride

Chloormethaan; Chlormethan; Chlorometan; Chloromethane; Cloreto de metila; Clorometano; Cloruro de metilo; Hlormetāns; Klormetan; Klórmetán; Methylchlorid; Metylklorid; Monochloromethane; Метилхлорид.
Chloromethane.
CH_3Cl=50.48
CAS — 74-87-3.
UNII — A6R43525YO.

Description. Methyl chloride is a colourless gas compressed to a colourless liquid with an ethereal odour. B.p. about -24 degrees. Store in airtight containers.

Uses

Methyl chloride is used as an industrial solvent. It has been used as an aerosol propellant and refrigerant and was formerly used as a local anaesthetic.

Adverse Effects and Treatment

Symptoms of methyl chloride intoxication often appear after a latent period of several hours and are similar after acute or chronic exposure to the vapour. Symptoms include gastrointestinal disturbances such as nausea, vomiting, and abdominal pain, and signs of CNS depression including headache, weakness, drowsiness, confusion, visual disturbances, and incoordination progressing to convulsions, coma, and death from respiratory depression in severe cases. There have been a few reports of hepatic and renal damage.

Treatment consists of removal from exposure and supportive and symptomatic measures. Neurological effects may persist for many months.

References to the toxicity of methyl chloride.

1. Repko JD, Lasley SM. Behavioral, neurological, and toxic effects of methyl chloride: a review of the literature. *CRC Crit Rev Toxicol* 1979; 6: 283–302.
2. IARC/WHO. Methyl chloride. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; 71: 737–47. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

Methyl Ethyl Ketone

Ethyl Methyl Ketone; Etilmetilcetona; Etylometyloketon; MEK; Metiletilcetona; Metyloetyloketon; Метилэтилкетон.
Butan-2-one.
C_4H_8O=72.11
CAS — 78-93-3.
UNII — 6PT9KLV9IO.

Description. Methyl ethyl ketone is a colourless flammable liquid with an acetone-like odour. Wt per mL about 0.81 g. B.p. 79 degrees to 81 degrees. Soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Uses

Methyl ethyl ketone is used as an industrial solvent and as an extraction solvent in food processing.

Adverse Effects

Methyl ethyl ketone is irritant. Inhalation may result in mild CNS effects including headache and dizziness; nausea and vomiting may also occur.

Methyl ethyl ketone may be implicated in volatile substance abuse (see under Toluene, p. 2216.3).

References.
1. WHO. Methyl ethyl ketone. *Environmental Health Criteria 143.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc143.htm (accessed 30/06/04)

Effects on the nervous system. There are isolated reports of neurotoxicity produced by methyl ethyl ketone alone.[1] These include 1 of retrobulbar neuritis and 1 of peripheral neuropathy. It has been suggested, however, that methyl ethyl ketone potentiates the peripheral neuropathy induced by methyl butyl ketone and *n*-hexane.

For further discussion of neurotoxicity after occupational exposure to solvents including methyl ethyl ketone, see under Toluene, p. 2216.2.

1. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; 8: 293–300.

Methylcellulose *(rINN)*

E461; Méthylcellulose; Methylcellulosum; Methylcelulosa; Metilcelliulozė; Metilcellulóz; Metilcelulosa; Metylcellulosa; Metyloceluloza; Metyyliselluloosa; Метилцеллюлоза.
CAS — 9004-67-5.
ATC — A06AC06.
ATC Vet — QA06AC06.

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

Ph. Eur. 8: (Methylcellulose). A cellulose having some of the hydroxyl groups in the form of the methyl ether. Various grades of methylcellulose are available and are distinguished by appending a number indicating the apparent viscosity in millipascal seconds of a 2% w/w solution at 20 degrees. It contains 26.0 to 33.0% of methoxy groups, calculated on the dried basis. It is a white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Practically insoluble in hot water, in dehydrated alcohol, in acetone, and in toluene; dissolves in cold water, forming a colloidal solution. A 2% w/w solution in water has a pH of 5.0 to 8.0.

USP 36: (Methylcellulose). A methyl ether of cellulose. When dried at 105 degrees for 2 hours, it contains 27.5 to 31.5% of methoxy groups. It is a white, fibrous powder or granules. It swells in water and produces a clear to opalescent, viscous, colloidal suspension; insoluble in alcohol, in chloroform, and in ether; soluble in glacial acetic acid and in a mixture of equal volumes of alcohol and chloroform. Its aqueous suspensions are neutral to litmus.

Incompatibility. Incompatibilities of methylcellulose have been reported with several compounds including chlorocresol, hydroxybenzoates, and phenol. Large amounts of electrolytes increase the viscosity of methylcellulose mucilages owing to salting-out of the methylcellulose; in very high concentrations of electrolytes, the methylcellulose may be completely precipitated.

Uses and Administration

The various grades of methylcellulose are widely used in pharmaceutical manufacturing as emulsifying, suspending, and thickening agents and as binding, disintegrating, and coating agents in tablet manufacturing. Low-viscosity grades are preferred for use as emulsifying agents as the surface tension produced is lower than with the higher-viscosity grades. Low-viscosity grades may also be used as suspending or thickening agents for liquid oral dosage forms and solutions of methylcellulose may be used as replacements for sugar-based syrups or other suspension bases. For thickening topically applied products such as gels and creams a high-viscosity grade is usually used. In tablet technology low- or medium-viscosity grades are used as binding agents while high-viscosity grades act as tablet disintegrants by swelling on contact with the disintegration medium. For tablet coating, highly substituted low-viscosity grades are usually used. Methylcellulose may also be included in modified-release tablet formulations.

Methylcellulose is also used as an emulsifier and stabiliser in the food industry.

Methylcellulose is used clinically as a bulk-forming agent. Medium- or high-viscosity grades are used as bulk laxatives in the treatment of constipation (p. 1804.3); by taking up moisture they increase the volume of the faeces and promote peristalsis. Methylcellulose is usually given in an oral dosage of up to 6 g daily in divided doses, taken with plenty of fluid. In the UK, the *BNFC* recommends a dose of 1 g twice daily for children aged from 7 to 12 years. Methylcellulose is also given in similar doses but with a minimum amount of water for the control of diarrhoea (p. 1805.2) and for the control of faecal consistency in ostomies. It is also used in the management of diverticular disease (p. 1806.2). Methylcellulose has also been used as an aid to appetite control in the management of obesity (p. 2315.1) but there is little evidence of efficacy.

Solutions of high-viscosity grade methylcellulose (usually 0.5 to 1%) have been used as a vehicle for eye

drops, as artificial tears, and in contact lens care, but hypromellose (p. 2189.3) is now generally preferred for this purpose.

Adverse Effects

Large quantities of oral methylcellulose may temporarily increase flatulence and distension and there is a risk of intestinal obstruction. Oesophageal obstruction may occur if compounds such as methylcellulose are swallowed dry.

Precautions

Methylcellulose and other bulk-forming agents should not be given orally to patients with intestinal obstruction or conditions likely to lead to intestinal obstruction. They should be taken with sufficient fluid to prevent faecal impaction or oesophageal obstruction, and should not be taken immediately before going to bed. Methylcellulose should not be used in infective bowel disease.

Interactions

Bulk laxatives such as oral methylcellulose lower the transit time through the gut and could affect the absorption of other drugs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Bulk†; ***Canad.***: Entrocel†; ***Irl.***: Celevac; ***Ital.***: Lacrimart; ***Spain***: Muciplazma; ***UK***: Celevac; ***USA***: Citrucel; Murocel†.

Multi-ingredient Preparations. ***Austral.***: 3B Beer Belly Buster†; Citri Slim+Trim†; ***Braz.***: Kolantyl DMP; Kolantyl; Kolantyl; ***Chile***: Vaselina Emulsionada; ***Fr.***: Lubri-Mucal; ***India***: Exxon; Fibropil; N-Zolin; NCZ; Nefacool; Ofet-H; ***Ital.***: Merankol Pastiglie; ***S.Afr.***: Kolantyl†; Merasyn†.

Pharmacopoeial Preparations
BP 2014: Methylcellulose Granules; Methylcellulose Tablets;
USP 36: Methylcellulose Ophthalmic Solution; Methylcellulose Oral Solution; Methylcellulose Tablets.

Microcrystalline Wax

Amorphous Wax; Cera microcristalina; Cerum microcrystallinum; Cire microcristalline; E905; INS No. 905c; Mikrokristályos Viasz; Petroleum Ceresin; Petroleum Wax (microcrystalline); Микрокристаллический Воск.
CAS — 63231-60-7.
UNII — XOF597Q3KY.

NOTE. The code E907 has been used for refined microcrystalline wax but is now used for hydrogenated polydecene (p. 2188.3).

Pharmacopoeias. In *USNF*.

USNF 31: (Microcrystalline Wax). A mixture of straight-chain, branched-chain, and cyclic hydrocarbons, obtained by solvent fractionation of the still bottom fraction of petroleum by suitable dewaxing or de-oiling means. A white or cream-coloured odourless waxy solid. Melting range 54 degrees to 102 degrees. Insoluble in water; sparingly soluble in dehydrated alcohol; soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils. Store in airtight containers.

Profile

Microcrystalline wax is used as a stiffening agent in creams and ointments and as a coating agent for solid dosage forms, including modified-release preparations. Microcrystalline wax is also used in foods and cosmetics.

Monoglyceride Citrate

E472c (citric acid esters of mono- and diglycerides of fatty acids).
CAS — 36291-32-4.

Pharmacopoeias. In *USNF*.

USNF 31: (Monoglyceride Citrate). A mixture of glyceryl mono-oleate and its citric acid monoester. It contains not less than 14.0% and not more than 17.0% total citric acid, calculated on the anhydrous basis. A soft white to ivory-coloured, waxy solid with a lard-like consistency and bland odour. Insoluble in water; dispersible in alcohol and in most common fat solvents.

Profile

Monoglyceride citrate is used as an emulsifier and as a stabiliser for antoxidants in the food industry.

Monophosphoryl Lipid A

Adeps A 3-*O*-Desacyl-4'-monophosphorylatus; 3-*O*-Desacyl-4'-monophosphoryl Lipid A; MPL.
UNII — MWC0ET1L2P.

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

Ph. Eur. 8: (3-*O*-Desacyl-4'-monophosphoryl lipid A). A detoxified derivative of the lipopolysaccharide (LPS) of ***Salmonella minnesota***, strain R595, which retains the immunostimulatory activities of the parent LPS. It consists of a mixture of congeners, all containing a backbone of β1'→6-linked disaccharide of 2-deoxy-2-aminoglucose phosphorylated at the 4'-position, but differing in the fatty acid substitutions at the 2, 2', and 3' positions. It is a lyophilised powder or a sterile liquid.

Profile

Lipopolysaccharides are important components of bacterial cell membranes and act as endotoxins, stimulating an immune response. Detoxified derivatives such as monophosphoryl lipid A are used as vaccine adjuvants, often combined with aluminium hydroxide. The immunostimulatory activities of monophosphoryl lipid A when combined with a vaccine include up-regulation of co-stimulatory molecules on antigen-presenting cells and secretion of pro-inflammatory cytokines, resulting in an enhanced immune response of the Th1-type against the antigens.

References.
1. Casella CR, Mitchell TC. Putting endotoxin to work for us: monophosphoryl lipid A as a safe and effective vaccine adjuvant. *Cell Mol Life Sci* 2008; 65: 3231–40.

Monosodium Glutamate

Chinese Seasoning; E621; Glutaman sodný; Glutamat monosòdic; Glutamate monosodique; Glutamato monossódico; Glutamato monossódico; Glutaminian sodu; Glutammato monosodico; Mononatrio glutamatas; Mononatriumglutamaat; Mononatriumglutamat; Monosodyum glutamat; MSG; Naatriumvesinikglutamaat; Natrii Glutamas; Natriumglutamaatti; Natriumglutamat; Nátrium-glutamát; Sodium Glutamate; Мононатриев глутамат; Глутамат Натрия; Глутамат-мононатрий.
Sodium hydrogen L-(+)-2-aminoglutarate monohydrate.
$C_5H_8NNaO_4.H_2O$=187.1
CAS — 142-47-2 (anhydrous monosodium glutamate).
UNII — W81N5U6R6U (monosodium glutamate); C3C196L9FG (anhydrous monosodium glutamate).

Pharmacopoeias. In *Chin.* Also in *USNF*.

USNF 31: (Monosodium Glutamate). White, practically odourless, free-flowing crystals or crystalline powder. It may have either a slightly sweet or slightly salty taste. Freely soluble in water; sparingly soluble in alcohol. pH of a 5% solution in water is between 6.7 and 7.2. Store in airtight containers.

Profile

Monosodium glutamate is widely used as a flavour enhancer and imparts a meaty flavour.

In susceptible individuals, ingestion of foods containing monosodium glutamate may cause MSG symptom complex, a condition characterised by burning sensations, or numbness, in the back of the neck and arms, tingling or warmth or weakness in the face, back and neck, facial pressure, chest pain, headache, nausea, drowsiness or weakness. In patients with asthma, who may be predisposed to develop this condition, bronchospasm may occur. The symptoms tend to occur within an hour of eating 3 g or more of monosodium glutamate on an empty stomach.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Wei Mei (味美).

Multi-ingredient Preparations. ***Chile***: Glutacyl Vitaminado; ***Ital.***: Dermitina; ***Thai.***: Hemo-Cyto-Serum†.

Musk

Almíscar; Almizcle; Deer Musk; Mesc; Misk; Mosc; Moschus; Musc; Muschio; Muskus; Muskusas; Mysk; Myski; Pižmo; Pižmo; Мускус.
CAS — 123-69-3 (musk); 541-91-3 (muskone).
UNII — 095I377U8F (musk); 8KFK4W7KP7 (musk sac resin); SJO79R759R (muskone).

Pharmacopoeias. In *Chin.*

Profile

Musk is the dried secretions from the preputial follicles of the musk deer, *Moschus moschiferus* or some other spp. of *Moschus* (Cervidae). It is used as a fragrance and fixative in perfumery. The main source of musk's fragrance is muskone (muscone).

A series of nitrated tertiary butyl toluenes or xylenes, or related compounds, are used as artificial musks. Musk ambrette, a synthetic nitromusk compound used in perfumery and as a food flavour, has been reported to cause contact dermatitis and photosensitivity.

Homoeopathy

Musk has been used in homoeopathic medicines under the following names: Moschus; Mosc.

References.
1. Schmeiser HH, *et al.* Evaluation of health risks caused by musk ketone. *Int J Hyg Environ Health* 2001; 203: 293–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ukr.***: Bezornil (Безорния).

Homoeopathic Preparations. ***Austria***: Ignatia-Homaccord; ***Cz.***: Hormeel S; Ypsiloheel; ***Hung.***: Hormeel S; ***Switz.***: Ignatia-Homaccord.

Myristic Acid

Kwas mirystynowy; 1-Tetradecanoic Acid; 1-Tridecanecarboxylic Acid; Миристиновая Кислота.
Tetradecanoic acid.
$C_{14}H_{28}O_2$=228.4
CAS — 544-63-8.
UNII — 0I3V7S25AW.

Pharmacopoeias. In *USNF*.

USNF 31: (Myristic Acid). It is obtained from coconut oil and other fats. A hard, white or faintly yellow, somewhat glossy, crystalline solid or a white or yellow-white powder. Congealing temperature between 48 degrees and 55.5 degrees. Practically insoluble in water; soluble in alcohol, in chloroform, and in ether.

Profile

Myristic acid is a saturated fatty acid with similar properties to palmitic acid (p. 2200.3). It is used in oral and topical pharmaceutical formulations.

Myristyl Alcohol

Alcohol miristilo; Alkohol mirystylowy; NSC-8549; 1-Tetradecanol; Миристиловый Спирт.
$C_{14}H_{30}O$=214.4
CAS — 112-72-1.
UNII — V42034O9PU.

Pharmacopoeias. In *USNF*.

USNF 31: (Myristyl Alcohol). M.p. 36 degrees to 42 degrees.

Profile

Myristyl alcohol is used as an oleaginous vehicle. Contact dermatitis has been associated with its use.

Neohesperidin Dihydrochalcone

E959; NCI-C60764; Neohesperidiinidihydrokalkoni; Neohesperidin DC; Neohesperidin-dihidrochalkonas; Neohesperidin-dihydrochalconum; Neohesperidin-dihydrochalkon; Neohesperidindivätekalkon; Neohesperidine DC; Neohesperidine dihydrochalcone; Néohespéridine-dihydrochalcone; Neoheszperidin-dihidro-kalkon; NHDC; Неогесперидин Дигидрохалкон.
3,5-Dihydroxy-4-[3-(3-hydroxy-4-methoxyphenyl)propionyl] phenyl 2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside.
$C_{28}H_{36}O_{15}$=612.6
CAS — 13241-33-3 (neohesperidin); 20702-77-6 (neohesperidin dihydrochalcone); 18916-17-1 (naringin dihydrochalcone); 65520-51-6 (neoeriocitrin dihydrochalcone).
UNII — OA5C88H3L0 (neohesperidin); 3X476D83QV (neohesperidin dihydrochalcone); 7233QDO0QW (naringin dihydrochalcone).

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

Ph. Eur. 8: (Neohesperidin-dihydrochalcone). A white or yellowish-white powder. Practically insoluble in water and in dichloromethane; freely soluble in dimethyl sulfoxide; soluble in methyl alcohol. Protect from light.

Profile

Neohesperidin dihydrochalcone is an intense sweetener derived from naringin, a flavonoid present in citrus peel. It is about 1000 to 1800 times as sweet as sucrose and is used in foods, beverages, and pharmaceuticals. It has a synergistic sweetening effect when used with other sweeteners.

Neotame

Neotaam; Neotam; Neotame; Neotamo; Neotaw; N-[N-(3,3-Dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

$C_{20}H_{30}N_2O_5$ = 378.5

CAS — 165450-17-9

UNII — V1597D52EX

Pharmacopoeias. In *USNF*.

USNF 31: (Neotame). Store in a dry place at a temperature not exceeding 40 degrees.

Profile

Neotame is an intense sweetener used in foods and beverages. It has between 7000 and 13 000 times the sweetening power of sucrose and is stable to heat.

References.

1. Anonymous. Neotame—a new artificial sweetener. *Med Lett Drugs Ther* 2002; 44: 73–4.

Nonoxinols

Macrogol Nonylphenyl Ethers; Nonoxinoles; Nonoxynols; Ноноксинолы.

α-(4-Nonylphenyl)-ω-hydroxypoly(oxyethylene).

CAS — 26027-38-3.

Nomenclature. Nonoxinols are a series of nonylphenyl ethers of macrogols of differing chain lengths, represented by the formula $C_{15}H_{23}.[O.CH_2.CH_2]_n.OH$.

Nonoxinol is *BAN* and *rINN*. The name may be followed by a figure indicating the approximate number of oxyethylene groups in the polyoxyethylene chain. *USAN* specifies Nonoxynol 4, Nonoxynol 9, Nonoxynol 15, and Nonoxynol 30.

Nonoxinol 9 *(BAN, rINN)*

Nonoksinol-9; Nonoksynol-9; Nonoxinol-9; Nonoxinolum 9; Nonoxynol 9 (USAN); Ноноксинол 9.

α-(4-Nonylphenyl)-ω-hydroxynona(oxyethylene).

$C_{33}H_{60}O_{10}$ (nominal)=616.8

UNII — 48QT80SH9T.

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

Ph. Eur. 8: (Nonoxinol 9). A mixture consisting mainly of monononylphenyl ethers of macrogols corresponding to the formula: $C_{15}H_{23}.(O.CH_2.CH_2)_n.OH$ where the average value of *n* is 9. A clear, colourless to light yellow, viscous liquid. Miscible with water, with alcohol, and with vegetable oils. Store in airtight containers.

USP 36: (Nonoxynol 9). An anhydrous liquid mixture consisting chiefly of monononylphenyl ethers of macrogols corresponding to the formula $C_{15}H_{23}.[O.CH_2.CH_2]n.OH$, in which the average value of *n* is about 9. A clear, colourless to light yellow, viscous liquid. Soluble in water, in alcohol, and in maize oil. Store in airtight containers.

Nonoxinol 10 *(BAN, rINN)*

Nonoxinolum 10; Nonoxynol 10; Ноноксинол 10.

α-(4-Nonylphenyl)-ω-hydroxydeca(oxyethylene).

$C_{35}H_{64}O_{11}$ (nominal)=660.9

UNII — K7O76887AP.

Nonoxinol 11 *(BAN, rINN)*

Nonoxinolum 11; Nonoxynol 11; Ноноксинол 11.

α-(4-Nonylphenyl)-ω-hydroxyundeca(oxyethylene).

$C_{37}H_{68}O_{12}$ (nominal)=704.9

Uses

Nonoxinols are macrogol aryl ether nonionic surfactants (p. 2164.2) used as solubilising agents. Nonoxinol 9 is used as a spermicide (see Contraception, p. 2232.3).

Antimicrobial activity. Nonoxinol 9 has activity *in vitro* against some bacteria and viruses and it was hoped[1,2] that use of spermicidal contraceptives containing nonoxinol 9 might provide some protection against sexually transmitted diseases, including chlamydial, gonococcal, and HIV infection. However, controlled studies involving HIV-negative female sex workers or other high-risk women have found that use of nonoxinol 9 does not reduce the rate of new HIV,[3,4] or gonorrhoea or chlamydia infection;[3,5] meta-analyses[6,7] including these and other studies have come to similar conclusions. Furthermore, nonoxinol 9 has an irritant action and may increase the risk of genital ulceration, leading to an increased risk of infection by HIV. The United Nations,[8] WHO,[9] and FDA[10] have therefore advised against its use by women at high risk.

1. North RB. Vaginal contraceptives: effective protection from sexually transmitted diseases for women? *J Reprod Med* 1988; 33: 307–311.
2. Anonymous. Multipurpose spermicides. *Lancet* 1992; 340: 211–13.
3. Roddy RE, *et al.* A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases. *N Engl J Med* 1998; 339: 504–10.
4. Van Damme L, *et al.* Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 2002; 360: 971–7. Correction. *ibid.*; 1892.
5. Roddy RE, *et al.* Effect of nonoxynol-9 gel on urogenital gonorrhea and chlamydial infection: a randomized controlled trial. *JAMA* 2002; 287: 1117–22.
6. Wilkinson D, *et al.* Nonoxynol-9 for preventing vaginal acquisition of HIV infection by women from men. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 21/04/08).
7. Wilkinson D, *et al.* Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 21/04/08).
8. Anonymous. UN warns against use of spermicide. *BMJ* 2000; 321: 194.
9. Anonymous. Nonoxinol 9 ineffective in preventing HIV infection. *WHO Drug Inf* 2002; 16: 120–1.
10. FDA. FDA mandates new warning for nonoxynol 9 OTC contraceptive products (issued 18/12/07). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109043.htm (accessed 23/08/10)

Contraception. A review[1] of the contraceptive use of nonoxinol 9. The antimotility and spermicidal properties of nonoxinols vary with their chain length: oligomers containing between 6 and 8 oxyethylene groups have the strongest effects on motility, while those with 8 to 10 units are the most spermicidal. The spermicidal action depends on lysis of sperm membranes resulting in detachment of the acrosome, midpiece, and neck, leading to immobilisation and cell death. Nonoxinol 9 is an effective spermicide at threshold concentrations of 100 micrograms/mL or above, and has been used for this purpose for more than 30 years in the form of over-the-counter creams, gels, foams, and condom lubricants. Studies have suggested that it is effective in preventing pregnancy in about 75% of cases. Factors contributing to failure may include inadequate concentration within cervical mucus (due to low partitioning from the aqueous phase and possibly micelle formation), and inadequate distribution in the vagina.

1. Iyer V, Poddar SS. Update on nonoxynol-9 as vaginal spermicide. *Eur J Contracept Reprod Health Care* 2008; 13: 339–50.

Adverse Effects and Precautions

Nonoxinols used as vaginal spermicides may cause local irritation.

Genito-urinary infections. Use of spermicidal foam or jelly containing nonoxinol 9 may disturb the normal vaginal flora and predispose to colonisation with *Escherichia coli* and the development of bacteriuria.[1] An increased risk of acute *E. coli* urinary-tract infection has been reported[2] associated with the use of condoms coated with nonoxinol 9. However, another study[3] of women using nonoxinol-9 spermicidal contraceptives showed that most users had minimal disruption to the vaginal microbial ecosystem.

For reference to an increased risk of some sexually transmitted diseases in women using nonoxinol 9, see Antimicrobial Activity, above.

1. Hooton TM, *et al.* Escherichia coli bacteriuria and contraceptive method. *JAMA* 1991; 265: 64–9.
2. Fihn SD, *et al.* Association between use of spermicide-coated condoms and Escherichia coli urinary tract infection in young women. *Am J Epidemiol* 1996; 144: 512–20.
3. Schreiber CA, *et al.* Effects of long-term use of nonoxynol-9 on vaginal flora. *Obstet Gynecol* 2006; 107: 136–43.

Pregnancy. Maternal use of spermicidal contraceptives has been linked to an increased frequency of congenital abnormalities, including trisomy, but it has been suggested that such studies may be flawed by recall bias.[1] Meta-analysis of 9 studies also supported the view that peri- and postconceptual maternal use of spermicides was not associated with adverse fetal outcome.[2]

1. Mishell DR. Contraception. *N Engl J Med* 1989; 320: 777–87.
2. Einarson TR, *et al.* Maternal spermicide use and adverse reproductive outcome: a meta-analysis. *Am J Obstet Gynecol* 1990; 162: 655–60.

Toxic shock syndrome. Toxic shock syndrome has been associated with the use of a vaginal contraceptive sponge impregnated with nonoxinol 9. A review[1] of 13 cases reported in the USA up to November 1984 found that in 4 of the cases there were other predisposing conditions: postpartum use, use during menstruation, and prolonged retention.

1. Faich G, *et al.* Toxic shock syndrome and the vaginal contraceptive sponge. *JAMA* 1986; 255: 216–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lorophyn; *Austral.*: Lubarol†; *Austria*: Patentex; *Braz.*: Preserv Nonoxinol-9; *Canad.*: Delfen†; Lifestyles†; Ortho-Gynol†; Ramses†; Trojan†; VCF†; *Chile*: Impidol; Supoviol; *China*: Ai Lv Shuang (爱侣栓); Lelemi (乐乐速); *Cz.*: Patentex Oval N†; *Fin.*: Patentex; *Ger.*: Patentex Oval; *Gr.*: Patentex; *Hong Kong*: Patentex†; VCF; *Hung.*: Patentex; *India*: Delfen†; *Irl.*: Ortho-Creme†; *Mex.*: Lorophyn†; *NZ*: Lifestyles; *Pol.*: Patentex Oval; Secural; *Port.*: Rendells; *Rus.*: Patentex Oval N (Патентекс Овал Н); Sterilin (Стерилин); *S. Afr.*: Delfen†; Gynol II†; *Turk.*: Lorophyn; *UK*: Gygel; Prelude; *USA*: Advantage 24; Delfen; Encare; Gynol II; Semicid; Sheik Elite; Shur-Seal; Today; VCF.

Multi-ingredient Preparations. *Arg.*: Merthiolate Iodopovidona; *Ger.*: A-gen 53†; *Hong Kong*: Protectaid; *Israel*: Glovan; Protectaid; *Mex.*: Sin-A-Gen; *Spain*: Lavolen†; *Turk.*: Agen; *UK*: Protectaid.

Octoxinols

Macrogol Tetramethylbutylphenyl Ethers; Octoxinoles; Octoxynols; Octylphenoxy Polyethoxyethanol; Октоксинолы.

α-[4-(1,1,3,3-Tetramethylbutyl)phenyl]-ω-hydroxypoly(oxyethylene).

CAS — 9002-93-1.

Nomenclature. Octoxinols are a series of tetramethylbutylphenyl ethers of macrogols of differing chain lengths, represented by the formula $C_{14}H_{21}.[O.CH_2.CH_2]_n.OH$.

Octoxinol is *BAN* and *rINN*. The name may be followed by a figure indicating the approximate number of oxyethylene groups in the polyoxyethylene chain. *USAN* specifies Octoxynol 9.

The name *p*-di-isobutyl-phenoxypolyethoxyethanol has been used to describe octoxinol 9 but may have also been applied to other octoxinols.

Octoxinol 9 *(BAN, rINN)*

Octoxinolum 9; Octoxynol 9 (USAN); Октоксинол 9.

$C_{32}H_{58}O_{10}$ (nominal)=602.8

Pharmacopoeias. In *USNF*.

USNF 31: (Octoxynol 9). An anhydrous liquid mixture consisting chiefly of mono[*p*-(1,1,3,3-tetramethylbutyl)] phenyl ethers of macrogols, corresponding to the formula $C_{14}H_{21}.[O.CH_2.CH_2]n.OH$, in which the average value of *n* is about 9. A clear, pale yellow, viscous liquid with a faint odour. Miscible with water, with alcohol, and with acetone; soluble in toluene and in benzene; practically insoluble in petroleum spirit. Store in airtight containers.

Octoxinol 10 *(BAN, rINN)*

Octoxinolum 10; Oktoksinoli-10; Oktoksinolis 10; Oktoksynol 10; Oktoxinol 10; Oktoxinol-10; Октоксинол 10.

$C_{34}H_{62}O_{11}$ (nominal)=646.9

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

Ph. Eur. 8: (Octoxinol 10). A mixture consisting mainly of mono-octylphenyl ethers of macrogols corresponding to the formula: $C_{14}H_{21}.(O.CH_2.CH_2)_n.OH$ where the average value of *n* is 10. A clear, colourless or light yellow, viscous liquid. Miscible with water, with alcohol, and with vegetable oils. Store in airtight containers.

Profile

Octoxinols are macrogol aryl ether nonionic surfactants (p. 2164.2) used as solubilising agents. They have also been used as spermicides.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Ortho-Gynol†; Summer's Eve Feminine; *NZ*: Ortho-Gynol†.

Multi-ingredient Preparations. *Austral.*: Summer's Eve Feminine; *Canad.*: Aseptone Quat.

Octyldodecanol

Octildodecanol; Octyldodecanol; Octyldodecanolum; Oktildodekanol; Oktildodekanolis; Oktyldodekanol; Oktylododekanol; Oktyylidodekanoli; Октилдеканол.

$C_{20}H_{42}O$=298.6

UNII — 461N1O614Y.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Octyldodecanol). A condensation product of saturated liquid fatty alcohols. It contains not less than 90% of (*RS*)-2-octyldodecan-1-ol, the remainder consisting

mainly of related alcohols. A clear, colourless to yellowish, oily liquid. Relative density 0.830 to 0.850. Practically insoluble in water; miscible with alcohol. Protect from light.

USNF 31: (Octyldodecanol). It contains not less than 90% of 2-octyldodecanol, the remainder consisting chiefly of related alcohols. A clear, water-white, free-flowing liquid. Insoluble in water; soluble in alcohol and in ether. Store in airtight containers.

Uses

Octyldodecanol is used as a pharmaceutical solvent.

Adverse Effects

Octyldodecanol can cause hypersensitivity reactions.

References.

1. Dharmagunawardena B, Charles-Holmes R. Contact dermatitis due to octyldodecanol in clotrimazole cream. *Contact Dermatitis* 1997; **36**: 231.
2. Dawn G, Forsyth A. Genital swelling caused by octyldodecanol contact dermatitis. *Clin Exp Dermatol* 2003; **28**: 228–9.
3. Singh M, *et al.* Contact sensitivity to octyldodecanol and trometamol in an anti-itch cream. *Contact Dermatitis* 2007; **56**: 289–90.

Oleic Acid

Acide oléique; Acido oleico; Acidum Oleicum; Elaic Acid; Kwas oleinowy; Kyselina olejová; Olajsav; Oleico, ácido; Oleinic Acid; Oleino rūgštis; Oleīnskābe; Oliezuur; Oljesyra; Oljesyre; Öljyhappo; Ölsäure; Масляная Кислота; Олеиновая Кислина; Олеиновая Кислота.

(*Z*)-9-Octadecenoic acid.

$C_{18}H_{34}O_2$=282.5

CAS — 112-80-1.

UNII — 2UMI9U37CP.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Oleic Acid). It contains 65 to 88% of oleic acid together with varying amounts of saturated and other unsaturated fatty acids. It may contain a suitable antoxidant. It is a clear, yellowish or brownish, oily liquid. Practically insoluble in water; miscible with alcohol and with dichloromethane. Store in well-filled airtight containers. Protect from light.

USNF 31: (Oleic Acid). It is manufactured from fats and oils derived from edible sources, animal or vegetable, and consists chiefly of oleic acid. It may contain suitable stabilisers. Oleic acid solely for external use is exempt from the requirement that it be prepared from edible sources. It is a colourless to pale yellow oily liquid when freshly prepared with a characteristic lard-like odour. On exposure to air it gradually absorbs oxygen and darkens in colour. When strongly heated in air, it is decomposed with the production of acid vapours. Congealing point between 3 degrees and 10 degrees for oleic acid from animal sources and between 10 degrees and 16 degrees for oleic acid from vegetable sources. Practically insoluble in water; miscible with alcohol, with chloroform, with ether, with benzene and with fixed and volatile oils. Protect from light. Avoid excessive heat.

Profile

Oleic acid forms soaps with alkaline substances and is used as an emulsifying or solubilising agent. It occurs in edible fats and oils which are used as foods or food components. Oleic acid is used in topical preparations, including transdermal films and patches, and in oral and inhalation preparations. It has also been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Glavit†; *Fr.*: Totephan†; *Ital.*: Esterol; *Singapore*: Natal Care.

Pharmacopoeial Preparations

BP 2014: Chloroxylenol Solution; White Liniment.

Oleyl Alcohol

Alcohol oleico; Alcohol oleicus; *cis*-9-Octadecen-1-ol; Oleic Alcohol; Oleilo alkoholis; Oléique (alcool); Oleo Alcohol; Oleol; Oleylalkohol; Oleyylialkoholi; Олеиловый Спирт.

(*Z*)-Octadec-9-en-1-ol.

$C_{18}H_{36}O$=268.5

CAS — 143-28-2.

UNII — 172F2WN8DV.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Oleyl Alcohol). A mixture of unsaturated and saturated long-chain fatty alcohols consisting mainly of oleyl alcohol and elaidyl alcohol; (*E*-octadec-9-en-1-ol; *trans*-9-octadecenol) It may be of vegetable or animal origin. A colourless or light yellow liquid.

USNF 31: (Oleyl Alcohol). A mixture of unsaturated and saturated high molecular weight fatty alcohols consisting chiefly of oleyl alcohol. A clear, colourless to light yellow, oily liquid with a faint characteristic odour. Insoluble in water; soluble in alcohol, in ether, in isopropyl alcohol, and in light liquid paraffin. Store in well-filled airtight containers at a temperature not exceeding 25 degrees.

Profile

Oleyl alcohol is used as an emollient, as an emulsifying and solubilising agent, and as a penetration enhancer in substances applied externally, including some delivered via transdermal patches. Oleyl alcohol has also been used in aerosol preparations for rectal use. The acetate has also been used.

Oleyl Oleate

Олеилолеат.

The oleyl ester of (*Z*)-9-octadecenoic acid.

$C_{36}H_{68}O_2$=532.9

CAS — 3687-45-4.

UNII — 3X3L452Y85.

Pharmacopoeias. In *Ger.* Also in *USNF.*

USNF 31: (Oleyl Oleate). It consists of esters of oleyl alcohol and high molecular weight fatty acids, principally oleic acid. A clear, colourless to light yellow liquid with a faint characteristic odour. Slightly soluble in alcohol; miscible with chloroform and with ether. Store in airtight containers.

Profile

Oleyl oleate is used as an emollient and emulsifying or solubilising agent in preparations for topical use.

Orange B

CI Acid Orange 137; Colour Index No. 19235; Naranja B; Оранжевый В.

The disodium salt of 1-(4-Sulfophenyl)-3-ethylcarboxyl-4-(4-sulfonaphthylazo)-5-hydroxypyrazole.

$C_{22}H_{16}N_4Na_2O_9S_2$=590.5

CAS — 15139-76-1.

UNII — RGU455O550.

Profile

Orange B is a synthetic azo dye used as a colouring agent in foods.

Palm Oil

Aceite de palma; Azeite de dendê; Huile de palme; Mawese; Minyak kelapa sawit; Olej palmowy; Oli de Palma; Olio di palma; Palmių aliejus; Palmöl; Palmolie; Palmolja; Palmový olej; Palmuõljy; Пальмовое Масло; Палмово Масло.

UNII — 5QUO05548Z (palm oil); 257TH8963H (hydrogenated palm oil).

Description. The crude oil is deep orange with a characteristic odour; it is semi-solid at 21 to 27 degrees.

Pharmacopoeias. In *USNF*, which also includes the hydrogenated oil.

USNF 31: (Palm Oil). It is obtained by refining the oil obtained from the pulp of the fruit of the oil palm *Elaeis guineensis*. A white to yellowish, fatty solid. Insoluble in water. Do not store above 55 degrees.

USNF 31: (Hydrogenated Palm Oil). It is obtained by refining and hydrogenating the oil obtained from the pulp of the fruit of the oil palm *Elaeis guineensis* and consists mainly of triglycerides of palmitic and stearic acids. A white to yellowish, fatty solid to semi-solid. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in ether. Store in airtight containers. Protect from light.

Palm Kernel Oil

Oleum Palmae Nuclei; Palm-nut Oil; Масло Пальмовое Косточковое; Пальмоядровое Масло.

CAS — 8023-79-8.

UNII — B0S90M0233.

Pharmacopoeias. In *USNF. Br.* includes the fractionated oil.

USNF 31: (Palm Kernel Oil). The refined fixed oil obtained from the kernels of the fruit of *Elaeis guineensis*. A white to yellowish, fatty solid. M.p. 27 degrees to 29 degrees. Insoluble in water. Store at a temperature not exceeding 45 degrees.

BP 2014: (Fractionated Palm Kernel Oil). It is obtained by expression of the natural oil from the kernels of *Elaeis guineensis* followed by selective solvent fractionation and hydrogenation. A white, odourless or almost odourless, solid, brittle fat. M.p. 31 degrees to 36 degrees. Practically insoluble in water and in alcohol; miscible with chloroform, with ether, and with petroleum spirit (boiling range, 40 degrees to 60 degrees). Store at a temperature not exceeding 25 degrees.

Profile

Palm oil is obtained from the fruit of the oil palm (*Elaeis guineensis*). Palm kernel oil is obtained from the kernels of the same species. The two substances have different characteristics and properties, although many of their uses are similar. Unrefined palm oil is rich in carotenoids, which are largely or wholly removed during standard refinement and processing.

Palm oil and palm kernel oil are produced and used worldwide on a large scale. Pharmaceutical applications of the oils or their derivatives include the compounding of creams and ointments, as a base for suppositories, and as a lubricant and binder in tablet and capsule formulation. They are also used in cooking and food processing and in the manufacture of a wide range of industrial and domestic products including soaps and cosmetics.

References.

1. Edem DO. Palm oil: biochemical, physiological, nutritional, hematological, and toxicological aspects: a review. *Plant Foods Hum Nutr* 2002; **57**: 319–41.
2. Sundram K, *et al.* Palm fruit chemistry and nutrition. *Asia Pac J Clin Nutr* 2003; **12**: 355–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Androlistica; Oxelio; Phytosolaire†; *Philipp.*: Livermin; *Singapore*: Androlistica.

Palmitic Acid *(USAN)*

Acide Palmitique; Acido palmitico; Acidum Palmiticum; Cetylic Acid; Hexadecansäure; Kwas palmitynowy; Kyselina palmitová; Palmitiinhape; Palmitiinihappo; Palmitik asit; Palmitinezuur; Palmitino rūgštis; Palmitinsäure; Palmitinsav; Palmitinsyra; Palmitinsyre; Palmitīnskābe; Пальмитиновая Кислота; Палмитинова киселина.

Hexadecanoic Acid.

$C_{16}H_{32}O_2$=256.4

CAS — 57-10-3.

UNII — 2V16EO95H1.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Palmitic Acid). A hexadecanoic acid ($C_{16}H_{32}O_2$ = 256.4), obtained from fats or oils of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in alcohol.

USNF 31: (Palmitic Acid). A mixture of solid organic acids obtained from fats or oils of animal or vegetable origin. It contains not less than 92% of $C_{16}H_{32}O_2$ and not more than 6% of stearic acid ($C_{18}H_{36}O_2$). A hard, white or faintly yellow, somewhat glossy crystalline solid, or white or yellowish-white powder. It has a slight characteristic odour and taste. Practically insoluble in water; soluble in alcohol, in chloroform, and in ether.

Profile

Palmitic acid is used as an emulsifying agent, skin penetration enhancer, and tablet and capsule lubricant.

Pectin

E440 (amidated pectin or pectin); Pectina; Pectine; Pektiin; Pektiini; Pektin; Pektyn; Пектин.

CAS — 9000-69-5.

ATC — A07BC01.

ATC Vet — QA07BC01.

UNII — 89NA02M4RX (pectin); O2ZUP321U8 (apple pectin); 47EQO8LE7H (citrus pectin).

Pharmacopoeias. In *US.*

USP 36: (Pectin). A purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace; it consists mainly of partially methoxylated polygalacturonic acids. A yellowish-white, almost odourless, coarse or fine powder. Almost completely soluble in 1 in 20 of water, forming a viscous, opalescent, colloidal solution which flows readily and is acid to litmus; practically insoluble in alcohol or in diluted alcohol and in other organic solvents. It dissolves more readily in water if first moistened with alcohol, glycerol, or simple syrup, or if mixed with 3 or more parts of sucrose. Store in airtight containers.

Uses and Administration

Pectin is a complex polysaccharide consisting mainly of partially methylated polygalacturonic acids and their salts. Pectins are important constituents of plant cell walls and contribute to dietary fibre (see under Dietary Role in Bran, p. 1823.3). They have a long history of use as emulsifiers, stabilisers, and gelling agents in the food industry.

Pectin is an adsorbent and bulk-forming agent and is present in multi-ingredient preparations for the management of diarrhoea, constipation, and obesity. Pectin has also been tried for reducing or slowing carbohydrate absorption in the dumping syndrome (p. 1806.2). Related compounds such as aluminium and magnesium polygalacturonate have also been used.

Interactions

Bulk-forming agents such as dietary fibre lower the transit time through the gut and may affect the absorption of other drugs.

Lipid regulating drugs. Pectin, used as a source of fibre, with a lipid-lowering diet and *lovastatin*, has resulted in a paradoxical increase in low-density lipoprotein (LDL)-cholesterol in patients with hypercholesterolaemia. It was believed the pectin reduced the absorption of lovastatin from the gut.[1]

1. Richter WO, *et al.* Interaction between fibre and lovastatin. *Lancet* 1991; 338: 706.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Arhemapectine Antihemorragique†.

Multi-ingredient Preparations. *Arg.*: Crema De Bismuto; Mucobase; *Austral.*: 3B Beer Belly Buster†; Betaine Digestive Aid; Citri Slim+Trim†; Diarcalm†; Diarezet†; Donnagel; Orabase; Psylli-Mucil Plus†; Stomahesive; Zellulean with Escin†; *Austria*: Diarrhoesan; *Belg.*: Tanalone; *Braz.*: Kaomagma; Parenterin; *Canad.*: Orabase; Orahesive; Tegasorb†; Watkins Settelz†; *Chile*: Enterol†; Purazolidona; *Fr.*: Piligel†; Gelopectose; Transifine; *Ger.*: Diarrhoesan; GoTa-Derm; *Gr.*: Kaopectate; Polypictine; *Hong Kong*: Diapectin†; Enterocin Compound†; Kaopectin; Pectolin†; Uni-Kaotin; *Indon.*: Andikap†; Arcapec; Diaend; Diagit; Entrogard; Envios; Kaopectate†; Licopec; Molagit; Neo Diaform; Neo Diastop; Neo Entrostop; Neo Kaocitin; Neo Kaolana; Neo Kaominal; Neo Koniform†; Opidiar; *Irl.*: Orabase†; *Israel*: Kaopectin; *Ital.*: Cruscasohn; Fibrovit; Nuleron; Streptomagma; *Mex.*: Ameban; Caopectar†; Colfur†; Colistin Magma†; Coraizul; Depofin; Dia-Par Compuesto; Dibapec Compuesto†; Estibal; Exofur; Pacetin-D; Parpectol; Puroxona CP; Isocar; K-Omistron; Kaomycin†; Kaopectate†; Kapecfuran; Kediar; Lactopectin†; Neokap; Neoxil; Nineka; Olam†; Optazol; Quimefuran; Suyodil; Treda; Yodozona; *NZ*: Orabase; Stomahesive; *S.Afr.*: Adco-Biskapect†; Betapect; Bipectinol†; Chloropect; Collodene†; Enterolyte; Gastropect; Granuflex; Granugel; Kantrexil; Kaostatex; Orabase†; Pectin-K†; Pectrolyte; *Singapore*: Apple Cider Vinegar Diet; Axcel Kaopec; Beakopectin; Bios Life; Diapectin; Pectolin; *Spain*: Dextricea†; Lupidon; *Switz.*: HEC†; *Thai.*: Biodan; Carbonpectate; Cenopect†; Diaropect; Difuran; Diocin; Disento PP; Puramed; Purasian; Puropectal; Puropectin; Kaolin Mixture w/ Pectin; Kaolin Mixture; Kaopectal; Kaptate; Patarlin; Profura; Suratin; *Turk.*: Streptomagma; *UAE*: Kaptin; *UK*: Goodypops; KLN; Orabase; Orahesive; Stomahesive; *USA*: Acidophilus with Citrus Pectin; Cepacol Sore Throat + Coating Relief Maximum Numbing; K-C; Kao-Paverin; Kao-Spen; Kaodene Non-Narcotic; Sucrets Herbal; *Venez.*: Klincosal; Micyn-2; Streptomagma.

Pentane

Amyl Hydride; Pentã; *n*-Pentaan; Pentaani; Pentan; Pentán; *n*-Pentane; Pentano; Pentans; Пентан.

C_5H_{12} = 72.15

CAS — 109-66-0.

UNII — 4FEV897A9T.

Profile

Pentane is used as a solvent and as a fuel. It is highly volatile and has also been used topically for its cooling effects.

References.

1. McKee R, *et al.* Toxicology of n-pentane (CAS no. 109-66-0). *J Appl Toxicol* 1998; 18: 431–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Prionex; *Hung.*: Deep Freeze; *UK*: Deep Freeze.

Petroleum Spirit

Benzina; Benzina de petróleo; Benzyna; Éter de petróleo; Light Petroleum; Ligroina; Nafta; Nafta de petróleo; Nafta de petróleo alifática; Petroleum Benzin; Petroleum Ether; Solvent Hexane; Петролейный эфир; бензин.

NOTE. The nomenclature for kerosene (p. 2191.1) and petroleum spirit is confusing and not always clearly distinguishable; in many languages similar terms are used for both.

Description. Petroleum spirit is a purified distillate of petroleum, consisting of a mixture of the lower members of the paraffin series of hydrocarbons. It is a colourless, transparent, very volatile, highly flammable liquid with a characteristic odour. It is available in a variety of boiling ranges.

Pharmacopoeias. In *Ger.*, *Jpn.*, and *Pol.* Various boiling ranges are specified.

Swiss describes Benzinum Medicinale, consisting mainly of hexane and heptane.

NOTE. The motor fuel termed 'petrol' in the UK and 'gasoline' in the USA is a mixture of volatile hydrocarbons of variable composition containing paraffins (alkanes), olefins (alkenes), cycloparaffins, and aromatic compounds.

Uses

Petroleum spirit and other petroleum distillates are used as pharmaceutical solvents.

Adverse Effects and Treatment

As for Kerosene, p. 2191.1. Petroleum spirit and petrol, being more volatile and of lower viscosity than kerosene, are more likely to be inhaled and to cause aspiration pneumonitis. The toxicity of petrol varies with its composition; some adverse effects have been attributed to lead additives or to the content of *n*-hexane or benzene. Petrol may be implicated in volatile solvent abuse (see under Toluene, p. 2216.3).

References to the toxicity of petroleum spirit.[1-5]

For discussion of neurotoxicity after occupational exposure to solvents including petrol, see under Toluene, p. 2216.2.

1. WHO. Selected petroleum products. *Environmental Health Criteria 20*. Geneva: WHO, 1982. Available at: http://www.inchem.org/documents/ehc/ehc/ehc020.htm (accessed 30/06/04)
2. Reese E, Kimbrough RD. Acute toxicity of gasoline and some additives. *Environ Health Perspect* 1993; 101 (suppl 6): 115–31.
3. Skalko RG. Reproductive and developmental toxicity of the components of gasoline. *Environ Health Perspect* 1993; 101 (suppl 6): 143–9.
4. Tenenbein M. Leaded gasoline abuse: the role of tetraethyl lead. *Hum Exp Toxicol* 1997; 16: 217–22.
5. Cairney S, *et al.* The neurobehavioural consequences of petrol (gasoline) sniffing. *Neurosci Biobehav Rev* 2002; 26: 81–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Travelex; Vertigopas; *Ger.*: Capillaron Vertigo; Kinolymphat†; Procordal vertigo; Steiroderm; Vertigopas; *Switz.*: Regenaplex Nr. 21e.

Phospholipids

Fosfolipidai; Fosfolipiden; Fosfolipidi; Fosfolipidos; Fosfolipidy; Fosfolipiidid; Fosfolipitler; Phosphatides; Phosphoacylglycérols; Phospholipide; Фосфолипиды; Фосфолипиди.

Pharmacopoeias. *USNF* includes egg phospholipids.

USNF 31: (Egg Phospholipids). It is a mixture of naturally occurring phospholipids obtained from the yolk of hens' eggs. Store at a temperature of -10 degrees or below under an atmosphere of nitrogen in airtight containers.

Profile

Phospholipids are naturally occurring lipids. They are amphiphilic molecules and are important components of cell membranes, partly due to their ability to form lipid bilayers; they also have emulsifying properties.

Most phospholipids are glycerophospholipids (phosphoglycerides) and consist of a glycerol backbone esterified with fatty acids and a phosphate group. Another group of phospholipids, phosphosphingolipids, have sphingosine, an amino-alcohol, as their backbone.

Phospholipids are generally obtained from sources such as egg yolk (egg phospholipids; egg phosphatides) or soya bean (soy phospholipids; soy phosphatides). They are used as emulsifying agents in pharmaceuticals and the food industry, and are also used to produce liposomal formulations. They are important constituents of pulmonary surfactants (p. 2599.2) used in neonatal respiratory distress syndrome. Lecithin (p. 2542.2), a mixture of phospholipids, and specific phospholipids such as phosphatidyl choline (p. 2588.3) and phosphatidyl serine (p. 2589.1), have been used as dietary supplements in many disorders. Highly purified phospholipid preparations, also known as essential phospholipids, are also used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Essliver (Эссливер); *Thai.*: Essentiale Forte.

Multi-ingredient Preparations. *Arg.*: Posfamina; Fosfotonic; Lipiforce; *Austria*: Essentiale; *Cz.*: Essentiale Forte N; *Fr.*: Lecitone; Optibiol; *Ger.*: Essentiale; *Hong Kong*: Essentiale; Physiogel; *India*: Mixo-EPL; *Indon.*: Hepabion†; Heparviton NF; Heparviton; Lecur; Lipimix; Nessiol; Procur Plus; Prolivit; Sensikol; Tripid; Vionin NF; *Ital.*: Leciplus; Memovigor; Nolder†; Vasobrain; *Malaysia*: Essentiale; Livolin; *Philipp.*: Essentiale Forte P; *Rus.*: Essentiale N (Эссенциале Н); Essliver Forte (Эссливер Форте); Phosphogliv (Фосфоглив); Phosphonciale (Фосфонциале); *S. Afr.*: Essentiale; *Singapore*: Essentiale; Livipids; Livolin; Manhae; Optibiol; *Spain*: Essavenon†; *Thai.*: Essaven; Essentiale; Essiver; Hepacap; *UK*: Emustil; *Ukr.*: Essentiale N (Эссенциале Н); Essliver Forte (Эссливер Форте); Farcovit B12 (Фарковит B12)†; Hepaforte (Гепафорте); Livolin Forte (Ливолин Форте); Phosphogliv (Фосфоглив); Venosan (Веносан).

Pigment Rubine

Brilliant Carmine 6B; Carmine 6B; CI Pigment Red 57; Colour Index No. 15850; Czerwień litolowa BK; E180; FD & C Red No. 7; Lithol Rubine BK; Litholrubin BK; Litholrubine BK; Litholrubintoner BKL; Litolrubin BK; Litolrubina BK; Permanent Rubin L6B; Pigmento rubí; Rubinpigment; Рубиновый Литол ВК.

Calcium 3-hydroxy-4-(4-methyl-2-sulfonatophenylazo)-2-naphthalene carboxylate.

$C_{18}H_{12}CaN_2O_6S$ = 424.4

CAS — 5281-04-9.

UNII — EEW0LZ41X8.

Profile

Pigment rubine is a synthetic azo dye used as a colouring agent for foodstuffs and cosmetics.

Polacrilin Potassium *(USAN, rINNM)*

Kalii Polacrilinum; Polacrilina potásica; Polacriline Potassique; Polacrilinum Kalii; Калия Полакрилин.

CAS — 54182-62-6 (polacrilin); 50602-21-6 (polacrilin).

UNII — 0BZ5A00FQU.

Pharmacopoeias. In *USNF*.

USNF 31: (Polacrilin Potassium). The potassium salt of a unifunctional low-cross-linked carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene. A white to off-white, free-flowing powder. Has a faint odour or is odourless. Insoluble in water and in most liquids.

Profile

Polacrilin potassium is used as a tablet and capsule disintegrant.

Poloxamers

Polioxietilen-propilenglicol; Poloksameerit; Poloksamerai; Poloxamera; Poloxamere; Poloxamerek; Poloxamerer; Poloxamères; Poloxámeros; Poloxamery; Polyethylene-polypropylene glycol; Полоксамеры.

α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene) poly(oxyethylene) block copolymer.

CAS — 9003-11-6.

Nomenclature. Poloxamer is *BAN* and *rINN*. The name is followed by a figure, the first 2 digits of which, when multiplied by 100, correspond to the approximate average molecular weight of the polyoxypropylene portion and the third digit, when multiplied by 10, corresponds to the percentage by weight of the polyoxyethylene portion. *USAN* specifies Poloxamer 182D, Poloxamer 182LF, Poloxamer 188, Poloxamer 188LF, and Poloxamer 331.

Poloxalene (*BAN, USAN, rINN*) is also a poloxamer.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Poloxamers). A synthetic block copolymer of ethylene oxide and propylene oxide represented by the general formula: $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. It may contain a suitable antoxidant. Poloxamer 124 is a colourless or almost colourless liquid. Poloxamer 237 and poloxamer 338 are white or almost white, waxy powders, microbeads or flakes; m.p. about 50 degrees. Poloxamers 124, 237, and 338 are very soluble in water and in alcohol; practically insoluble in petroleum spirit (50 degrees to 70 degrees). pH of a 10% solution in water is 5.0 to 7.5. Store in airtight containers.

USNF 31: (Poloxamer). A synthetic block copolymer of ethylene oxide and propylene oxide with the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. It may contain a suitable antoxidant. Poloxamer 124 is a colourless liquid with a mild odour. Poloxamers 237 and 338 are white, prilled or cast solids, odourless or with a mild odour. All poloxamers are freely soluble in water and in alcohol. Poloxamer 124 is freely soluble in isopropyl alcohol and in propylene glycol; poloxamer 237 is sparingly soluble in isopropyl alcohol and in xylene; poloxamer 338 is sparingly soluble in propylene glycol; poloxamer 124 is freely soluble in xylene. A 2.5% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

Incompatibility. Poloxamers have been reported to be *incompatible with hydroxybenzoates and phenols.*

Poloxalene *(BAN, USAN, rINN)*

Poloxalène; Poloxaleno; Poloxalenum; SKF-18667; Полоксален.

CAS — 9003-11-6.
UNII — V883K56SW0.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Poloxalene). A synthetic block copolymer of ethylene oxide and propylene oxide. A colourless or pale yellow liquid. Soluble in water, in chloroform, and in ethylene dichloride. A 2.5% solution in water has a pH of 5.0 to 7.5. Store in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Poloxamer 188 *(BAN, USAN, rINN)*

Poloxalkol; Poloxamère 188; Poloxámero 188; Poloxamerum 188; Полоксамер 188.

UNII — LQA786G8JG.

NOTE. Compounded preparations of poloxamer 188 may be represented by the following names:

- Co-danthramer *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of dantron and poloxamer respectively.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Poloxamers). Poloxamer 188 is a poloxamer in which *a* in the general formula given on p. 2201.3 is 75 to 85 and *b* is 25 to 30; it has an average molecular weight of 7680 to 9510. It is a white or almost white, waxy powder, microbeads, or flakes. M.p. about 50 degrees. Very soluble in water and in alcohol; practically insoluble in petroleum spirit (50 degrees to 70 degrees). pH of a 10% solution is 5.0 to 7.5. Store in airtight containers.

USNF 31: (Poloxamer). Poloxamer 188 is a poloxamer in which *a* in the general formula averages 80 and *b* averages 27; it has an average molecular weight of 7680 to 9510. A white prilled or cast solid, odourless or with a very mild odour. M.p. about 52 degrees. Freely soluble in water and in alcohol. Store in airtight containers.

Poloxamer 407 *(BAN, rINN)*

Poloxamère 407; Poloxámero 407; Poloxamerum 407; Полоксамер 407.

UNII — TUF2NW3M2.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Poloxamers). Poloxamer 407 is a poloxamer in which *a* in the general formula given on p. 2201.3 is 95 to 105 and *b* is 54 to 60; it has an average molecular weight of 9840 to 14 600. It is a white or almost white, waxy powder, microbeads, or flakes. M.p. about 50 degrees. Very soluble in water and in alcohol; practically insoluble in petroleum spirit (50 degrees to 70 degrees). pH of a 10% solution in water is 5.0 to 7.5. Store in airtight containers.

USNF 31: (Poloxamer). Poloxamer 407 is a poloxamer in which *a* in the general formula averages 101 and *b* averages 56; it has an average molecular weight of 9840 to 14 600. A white, prilled or cast solid, odourless or with a very mild odour. M.p. about 56 degrees. Freely soluble in water, in alcohol, and in isopropyl alcohol. Store in airtight containers.

Uses and Administration

Poloxamers are copolymer nonionic surfactants (p. 2164.2). They are used as emulsifying agents for intravenous fat emulsions, as solubilising agents to maintain clarity in elixirs and syrups, and as wetting agents for antibacterials. They may also be used in ointment or suppository bases and as tablet binders or coaters.

Poloxamer 188 is used as a wetting agent in the treatment of constipation, usually with a laxative such as dantron. It has also been used as an emulsifying agent in fluorocarbon blood substitutes. It is thought to have effects on blood flow and cellular repair and has been investigated in sickle-cell crisis, myocardial infarction, and burns.

Poloxamer 407 is used in solutions for contact lens care, as is poloxamer 338.

Poloxalene is used as a defoaming agent in the treatment of bloat in ruminants.

References.

1. **Orringer EP, *et al.*** Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: a randomized controlled trial. *JAMA* 2001; 286: 2099–2106.
2. Gibbs WJ, Hagemann TM. Purified poloxamer 188 for sickle cell vaso-occlusive crisis. *Ann Pharmacother* 2004; 38: 320–4.
3. Dumortier G, *et al.* A review of poloxamer 407 pharmaceutical and pharmacological characteristics. *Pharm Res* 2006; 23: 2709–28.

Precautions

Poloxamers may increase the absorption of liquid paraffin and other fat-soluble substances.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Coloxyl; *NZ*: Coloxyl; *S.Afr.*: Pliagel†.

Multi-ingredient Preparations. *Arg.*: Natura Confort; *Ger.*: Linola Wundgel; *Irl.*: Ailax†; Codalax; Cotron; *Malaysia*: Cationorm; *NZ*: Pinorax; *Rus.*: Peritoran (Периторан); *Singapore*: Listerine Bright & Clean; Listerine Cool Citrus; *Thai.*: Siduol; *UK*: Codalax; Danlax; *USA*: Baby Orajel Tooth and Gum Cleanser; ControlRx.

Polydextrose *(USAN)*

CP-31081; E1200; Polidextrosa; Polydekstroosi.

CAS — 68424-04-4.
UNII — VH2XOU12IE.

Pharmacopoeias. *USNF* includes Polydextrose and Hydrogenated Polydextrose

USNF 31: (Polydextrose). A randomly branched polymer prepared by melting and subsequent condensation of the ingredients, which consist of approximately 90 parts glucose, 10 parts sorbitol, and up to 1 part citric acid or 0.1 part phosphoric acid. The 1,6-glycosidic linkage predominates in the polymer but other linkages are present. It contains small quantities of free glucose, sorbitol, and 1,6-anhydro-D-glucose (levoglucosan), with traces of citric acid or phosphoric acid. An off-white to light tan-coloured solid. Very soluble in water; insoluble in alcohol; slightly soluble in glycerol and in propylene glycol. A 10% solution has a pH of 2.5 to 5.0. Store in airtight containers at a temperature between 8 degrees and 15 degrees. Protect from light and moisture.

USNF 31: (Hydrogenated Polydextrose). Hydrogenated Polydextrose is obtained by transition metal catalytic hydrogenation of Polydextrose in aqueous solution. It contains not less than 90.0% of glucose polymer units, calculated on the anhydrous and ash-free basis. The polymer chain end groups are mainly sorbitol-terminated. An off-white to light tan-coloured solid. Very soluble in water; soluble in alcohol; slightly soluble in glycerol and in propylene glycol. A 10% solution has a pH of 5.0 to 7.0. Store in airtight containers at a temperature between 8 degrees and 15 degrees. Protect from light and moisture.

Profile

Polydextrose is a random polymer of glucose used as a bulking agent, binder, and coating agent in pharmaceutical preparations. It is also used as a low-calorie carbohydrate bulking agent in the food industry.

Polyethylene Oxide

Polietileno, óxido de; Полиэтилен Оксид.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyethylene Oxide). A nonionic homopolymer of ethylene oxide, represented by the formula $H(OCH_2CH_2)_nOH$, in which *n* represents the average number of oxyethylene groups (about 2000 to 200 000). It is obtainable in several grades, varying in viscosity profile in an aqueous isopropyl alcohol solution. It may contain not more than 3% of silicon dioxide. A white to off-white powder. Miscible with water; freely soluble in acetonitrile, in dichloromethane, in ethylene dichloride, and in trichloroethylene; insoluble in aliphatic hydrocarbons, in ethylene glycol, in diethylene glycol, and in glycerol. Store in airtight containers. Protect from light.

Profile

Polyethylene oxide is a high-molecular-weight macrogol (p. 2547.3) used as a tablet binder and as a suspending and thickening agent in pharmaceutical preparations. Polyethylene oxide has been used in hydrogel wound dressings.

Polyisobutylene



Polyisobutene; Полиизобутилен.

2-Methyl-1-propene homopolymer.

$(C_4H_8)_x$

CAS — 9003-27-4.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyisobutylene). A synthetic polymer produced by the low-temperature polymerisation of isobutylene in liquid ethylene, dichloromethane, or hexane, using an aluminium chloride or boron trifluoride catalyst. It may contain a suitable stabiliser. Grades are characterised by the range of intrinsic viscosity or the range for the Staudinger Index.

Low molecular-weight grades are soft and gummy; high molecular-weight grades are tough and elastic. All grades are light in colour, odourless, and tasteless. Insoluble in water; soluble in chloroform, in di-isobutylene, and in toluene.

Profile

Polyisobutylene is a synthetic polymer available in a range of molecular weights. It is used as an adhesive in transdermal patches, and has many other industrial applications.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Stomahesive; *UK*: Stomahesive.

Polyoxyl Castor Oils

Aceites de ricino polioxietilenados; Glycerol Polyethylene Glycol Ricinoleate; Macrogol Glycerol Ricinoleates; Macrogolglycerol Ricinoleate; Macrogolglycérol, ricinoléate de; Macrogolglycerolі ricinoleas; Macrogolglycerolricinoleat; Makrogol-glicerin-éter -ricinoleát; Makrogolglicerólio ricinoleatas; Makrogolglycerolricinoleat; Makrogoliglyserolrisiinioleaatti; Makrogologlicerolu rycynooleinian; PEG Glyceryl Ricinoleates; Polyethoxylated Castor Oils; Polyethylene Glycol Glyceryl Ricinoleates; Polyoxyethylene Castor Oils; Polyoxyethylene Glyceryl Ricinoleates; Полиэтиленгликоля Касторовые Масла.

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

Ph. Eur. 8: (Macrogolglycerol Ricinoleate; Polyoxyl Castor Oil BP 2014). It contains mainly ricinoleyl glycerol ethoxylated with 30 to 50 molecules of ethylene oxide (nominal value), with small amounts of macrogol ricinoleate and of the corresponding free glycols. It results from the reaction of castor oil with ethylene oxide. A clear, yellow, viscous liquid or semi-solid. Relative density about 1.05; viscosity, at 25 degrees, 500 to 800 mPa s. Freely soluble in water and in alcohol; very soluble in dichloromethane. Protect from light.

Polyoxyl 35 Castor Oil

Aceite de ricino polioxil 35; Полиэтиленгликоля 35 Касторовое Масло.

UNII — 6D4M1DAL6O.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyoxyl 35 Castor Oil). A mixture of the triricinoleate ester of ethoxylated glycerol with smaller amounts of macrogol ricinoleate and the corresponding free glycols. It is produced by reacting 1 mole of glycerol ricinoleate with about 35 moles of ethylene oxide.

A yellow oily liquid with a faint characteristic odour. Sp. gr. 1.05 to 1.06; viscosity, at 25 degrees, 650 to 850 mPa s. Very soluble in water, producing a practically odourless and colourless solution; soluble in alcohol and in ethyl acetate; insoluble in mineral oils. Store in airtight containers.

Incompatibility. Polyoxyl castor oils are reported to affect PVC containers and apparatus adversely.

Uses

Polyoxyl castor oils are ethoxylated glycerol ester nonionic surfactants (p. 2164.2) used as emulsifying and solubilising agents. Polyoxyl 35 castor oil has been used as a solvent in vehicles for various intravenous injections.

Adverse Effects

Polyoxyl castor oils (such as *Cremophor EL*) used as vehicles in intravenous injections have been associated with severe anaphylactoid reactions, hyperlipidaemias, alterations in blood viscosity, and erythrocyte aggregation. They may also

lead to adverse effects due to alterations in the pharmacokinetics of the formulated drug.

References.
1. Bagnarello AG, *et al.* Unusual serum lipoprotein abnormality induced by the vehicle of miconazole. *N Engl J Med* 1977; 296: 497–9.
2. Forrest ARW, *et al.* Long-term Althesin infusion and hyperlipidaemia. *BMJ* 1977; 2: 1357–8.
3. Dye D, Watkins J. Suspected anaphylactic reaction to Cremophor EL. *BMJ* 1980; 280: 1353.
4. Howrie DL, *et al.* Anaphylactoid reactions associated with parenteral cyclosporine use: possible role of Cremophor EL. *Drug Intell Clin Pharm* 1985; 19: 425–7.
5. Chapuis B, *et al.* Anaphylactic reaction to intravenous cyclosporine. *N Engl J Med* 1985; 312: 1259.
6. Siddall SJ, *et al.* Anaphylactic reactions to teniposide. *Lancet* 1989; i: 394.
7. ten Tije AJ, *et al.* Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. *Clin Pharmacokinet* 2003; 42: 665–85.
8. Hennenfent KL, Govindan R. Novel formulations of taxanes: a review. Old wine in a new bottle? *Ann Oncol* 2006; 17: 735–49.

Polyoxyl Hydrogenated Castor Oils

Aceites de ricino hidrogenados y polioxietilenados; Ethoxylated Hydrogenated Castor Oils; Glycerol Polyethylene Glycol Hydroxystearates; Macrogolglycerol Hydroxystearate; Macrogolglycérol, hydroxystéarate de; Macrogolglycerolhydroxystearat; Macrogolglycerol hydroxystearas; Macrogrol Glicerol Hydroxystearates; Makrogol-glicerin-éter-hidroxiszterarát; Makrogolglicerolio idrossistearato; Makrogeliglyserolhydroxistearat; Makrogoliglyserolihydroksistearaatti; PEG Hydrogenated Castor Oils; Polyethylene Glycol Hydrogenated Castor Oils; Polyoxyethylene Hydrogenated Castor Oils; Полиэтиленгликоля Касторовые Масла Гидрогенизированные.

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

Ph. Eur. 8: (Macrogolglycerol Hydroxystearate; Hydrogenated Polyoxyl Castor Oil BP 2014). It contains mainly trihydroxystearyl glycerol ethoxylated with 7 to 60 molecules of ethylene oxide (nominal value), with small amounts of macrogol hydroxystearate and of the corresponding free glycols. It results from the reaction of hydrogenated castor oil with ethylene oxide. Polyoxyl hydrogenated castor oil with less than 10 units of ethylene oxide per molecule is a yellowish, turbid, viscous liquid. Practically insoluble in water; dispersible in alcohol; soluble in acetone. Polyoxyl hydrogenated castor oil with more than 20 units of ethylene oxide per molecule is a white or yellowish, semi-liquid or pasty mass. Freely soluble in water, in alcohol, and in acetone; practically insoluble in petroleum spirit.

Polyoxyl 40 Hydrogenated Castor Oil

Aceite de ricino hidrogenado polioxil 40; Полиэтиленгликоля 40 Касторовое Масло Гидрогенизированное.

UNII — 7YC586QO8C

Pharmacopoeias. In *USNF*.

USNF 31: (Polyoxyl 40 Hydrogenated Castor Oil). A mixture of mainly the trihydroxystearate ester of ethoxylated glycerol, with smaller amounts of macrogol trihydroxystearate and the corresponding free glycols. It is produced by reacting 1 mole of glycerol trihydroxystearate with about 40 to 45 moles of ethylene oxide.

A white to yellowish paste or pasty liquid with a faint odour. Congealing range 20 degrees to 30 degrees. Very soluble in water, producing an odourless, colourless solution; soluble in alcohol and in ethyl acetate; insoluble in liquid paraffin. Store in airtight containers.

Profile

Polyoxyl hydrogenated castor oils are ethoxylated glycerol ester nonionic surfactants (p. 2164.2). They are used as solubilisers and emulsifiers in oral and topical pharmaceutical preparations; they are also used in cosmetics.

Polysorbates

Macrogol Sorbitan Esters; Polisorbatos; Polyethylene Glycol Sorbitan Esters; Polyoxyethylene Sorbitan Esters; Sorbimacrogols; Полисорбаты.

Description. Polysorbates are polyoxyethylene derivatives of cyclic sorbitol anhydrides partially esterified with a fatty acid. The numbered polysorbates listed as *BAN*, *INN*, and *USAN* are polyoxyethylene 20 sorbitan esters, in which each mole of sorbitan is ethoxylated with about 20 moles of ethylene oxide.

Incompatibility. Polysorbates have been reported to be stable with electrolytes and weak acids and bases although saponification may occur in the presence of strong acids and bases. Discoloration or precipitation may occur with phenolic substances. The oleic acid esters are sensitive to oxidation. For reference to the possible incompatibility of polysorbate 80 with hydroxybenzoates, see p. 1757.3.

Polysorbate 20 *(BAN, USAN, rINN)*

E432; Monolaurato de polietileno 20 sorbitano; Monolaurato de polioxietileno 20 sorbitano; Polisorbat 20; Polisorbatas 20; Polisorbato 20; Poliszorbát 20; Polyoxyethylene 20 Sorbitan Monolaurate; Polysorbaatti 20; Polysorbat 20; Polysorbate 20; Polysorbatum 20; Sorbimacrogol Laurate 300; Sorboxaethenum Lauricum; Полисорбат 20.

$C_{58}H_{114}O_{26}$(approximate)

CAS — 9005-64-5.

UNII — 7T1F30V5YH.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF*.

Ph. Eur. 8: (Polysorbate 20). A mixture of partial esters of fatty acids, mainly lauric acid, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A clear or slightly opalescent yellowish to brownish-yellow oily liquid. Relative density about 1.10. Soluble in water, in dehydrated alcohol, in ethyl acetate, and in methyl alcohol; practically insoluble in liquid paraffin and in fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Polysorbate 20). A laurate ester of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A lemon to amber liquid with a faint characteristic odour. Soluble in water, in alcohol, in dioxan, in ethyl acetate, and in methyl alcohol; insoluble in liquid paraffin. Store in airtight containers.

Polysorbate 40 *(BAN, USAN, rINN)*

E434; Monopalmitato de polietileno 20 sorbitano; Monopalmitato de polioxietileno 20 sorbitano; Polisorbatas 40; Polisorbato 40; Poliszorbát 40; Polyoxyethylene 20 Sorbitan Monopalmitate; Polysorbaatti 40; Polysorbat 40; Polysorbate 40; Polysorbatum 40; Sorbimacrogol Palmitate 300; Полисорбат 40.

$C_{62}H_{122}O_{26}$(approximate)

CAS — 9005-66-7.

UNII — STJ1I8SA2X.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Polysorbate 40). Mixture of partial esters of fatty acids, mainly palmitic acid, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides. An oily, viscous, yellowish or brownish-yellow liquid. Relative density about 1.10. Miscible with water, with dehydrated alcohol, with ethyl acetate, and with methyl alcohol; practically insoluble in fatty oils and in liquid paraffin. Store in airtight containers. Protect from light.

The BP 2014 gives Polyoxyethylene 20 Sorbitan Monopalmitate as an approved synonym.

USNF 31: (Polysorbate 40). A palmitate ester of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A yellow liquid with a faint characteristic odour. Soluble in water and in alcohol; insoluble in liquid paraffin and in vegetable oils. Store in airtight containers.

Polysorbate 60 *(BAN, USAN, rINN)*

E435; Monoestearato de polietileno 20 sorbitano; Monoestearato de polioxietileno 20 sorbitano; Polisorbat 60; Polisorbatas 60; Polisorbato 60; Poliszorbát 60; Polyoxyethylene 20 Sorbitan Monostearate; Polysorbaatti 60; Polysorbat 60; Polysorbát 60; Polysorbatum 60; Sorbimacrogol Stearate 300; Sorboxaethenum Stearinicum; Полисорбат 60.

$C_{64}H_{126}O_{26}$(approximate)

CAS — 9005-67-8.

UNII — CAL22UVI4M.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF*.

Ph. Eur. 8: (Polysorbate 60). A mixture of partial esters of fatty acids, mainly stearic acid 50, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A yellowish-brown gelatinous mass which becomes a clear liquid at temperatures above 25 degrees. Relative density about 1.10. Soluble in water, in dehydrated alcohol, in ethyl acetate, and in methyl alcohol; practically insoluble in liquid paraffin and in fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Polysorbate 60). A mixture of stearate and palmitate esters of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A lemon to orange-coloured oily liquid or semi-gel with a faint characteristic odour. Soluble in water, in ethyl acetate, and in toluene; insoluble in liquid paraffin and in vegetable oils. Store in airtight containers.

Polysorbate 80 *(BAN, USAN, rINN)*

E433; Monooleato de polietileno 20 sorbitano; Monooleato de polioxietileno 20 sorbitano; Olethytan 20; Polisorbat 80; Polisorbatas 80; Polisorbato 80; Poliszorbát 80; Polyäthylenglykol-Sorbitanoleat; Polyoxyethylene 20 Sorbitan Monooleate; Polysorbaatti 80; Polysorbat 80; Polysorbate 80; Polysorbatum 80; Polysorbitanum 80 Oleinatum; Sorbimacrogol Oleate 300; Sorboxaethenum Oleinicum; Sorethytan 20 Mono-oleate; Полисорбат 80.

$C_{64}H_{124}O_{26}$(approximate)

CAS — 9005-65-6.

UNII — 6OZP39ZG8H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Polysorbate 80). A mixture of partial esters of fatty acids, mainly oleic acid, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. An oily, colourless or brownish-yellow, clear or slightly opalescent liquid. Relative density about 1.10. Dispersible in water, in dehydrated alcohol, in ethyl acetate, and in methyl alcohol; practically insoluble in liquid paraffin and in fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Polysorbate 80). An oleate ester of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A lemon to amber-coloured oily liquid with a faint characteristic odour. Sp. gr. between 1.06 and 1.09; viscosity, at 25 degrees, between 300 and 500 mPa s. Very soluble in water, producing an odourless and practically colourless solution; soluble in alcohol and in ethyl acetate; insoluble in liquid paraffin. Store in airtight containers.

Polysorbate 85 *(BAN, USAN, rINN)*

Polisorbatas 85; Polisorbato 85; Poliszorbát 85; Polyoxyethylene 20 Sorbitan Trioleate; Polysorbaatti 85; Polysorbat 85; Polysorbate 85; Polysorbatum 85; Sorbimacrogol Trioleate 300; Trioleato de polietileno 20 sorbitano; Trioleato de polioxietileno 20 sorbitano; Полисорбат 85.

$C_{100}H_{188}O_{28}$(approximate)

CAS — 9005-70-3.

UNII — A7F3N56197.

Description. A mixture of mainly trioleate esters of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides.

Uses

Polysorbates are ethoxylated sorbitan ester nonionic surfactants (p. 2164.2). They usually correspond to polyoxyethylene 20 sorbitan esters, in which each mole of sorbitan is ethoxylated with about 20 moles of ethylene oxide, although polysorbates with different ethoxylation ratios may also be used. The number following polysorbate in the name relates to both the ethoxylation ratio and the fatty acid component of the sorbitan ester.

Polysorbates are hydrophilic and are used as emulsifying agents for the preparation of stable oil-in-water emulsions in pharmaceutical products; they are frequently used with a sorbitan ester in varying proportions to produce products with a range of texture and consistency. Polysorbates have also been used in the formulation of insecticide and herbicide sprays, industrial detergents, and cosmetic products. They are also used as emulsifiers in the food industry.

Polysorbates are used as solubilising agents for a variety of substances including essential oils and oil-soluble vitamins such as vitamins A, D, and E, and as wetting agents in the formulation of oral and parenteral suspensions. However, hypersensitivity reactions have been attributed to the presence of polysorbates, see Hypersensitivity, p. 2204.1.

Polysorbates may also be used for their surfactant properties in preparations for the removal of ear wax, and for the management of dry eyes and upper respiratory-tract disorders.

Adverse Effects and Precautions

Polysorbates may increase the absorption of fat-soluble substances.

There have been occasional reports of hypersensitivity after topical application of preparations containing polysorbates.

For discussion of fatalities in low-birth-weight infants associated with the injection of a polysorbate-containing preparation, see p. 2204.1.

Polysorbates used as excipients may also lead to adverse effects due to alterations in the pharmacokinetics of the formulated drug.

References.
1. ten Tije AJ, *et al.* Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. *Clin Pharmacokinet* 2003; 42: 665–85.

Effects in infants. After the introduction in the USA of an intravenous preparation of vitamin E (*E-Ferol*) there were a number of reports of unusual liver and kidney disorders, with 38 deaths being reported among treated low-birth-weight infants. Affected infants had unexplained hypotension, thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, and metabolic acidosis;[1-3] the preparation was subsequently withdrawn from the market in April 1984 about 5 months after it was introduced. *In-vitro* evidence was produced showing that *E-Ferol* suppressed the response of human lymphocytes to phytohaemagglutinin. However, it was the mixture of polysorbates, polysorbate 20 and in particular polysorbate 80, that was shown to be responsible for this suppression rather than the α-tocopherol acetate component. Despite this *in-vitro* data, overwhelming infection was not a feature in the affected infants.[2] Large doses of polysorbates were unavoidably injected when *E-Ferol* was used and it was suggested that polysorbates may accumulate as a result of an alteration in the metabolism by low-birth-weight infants; polysorbate-induced alteration of membrane fluidity in cells of vessel walls may have led to changes in structure and function.[2]

Polysorbate 80 was also suggested as part of the cause of a severe hypotensive episode in an infant given an intravenous overdose of amiodarone; benzyl alcohol in the formulation may also have contributed.[4]

1. Allade SL, *et al.* Polysorbate 80 and E-Ferol toxicity. *Pediatrics* 1986; 77: 593–7.
2. Ballstreri WF, *et al.* Lessons from the E-Ferol tragedy. *Pediatrics* 1986; 78: 503–6.
3. Golightly LK, *et al.* Pharmaceutical excipients: adverse effects associated with inactive ingredients in drug products. *Med Toxicol* 1988; 3: 128–65 and 209–240.
4. Masi S, *et al.* Acute amiodarone toxicity due to an administration error: could excipient be responsible? *Br J Clin Pharmacol* 2009; 67: 691–3.

Hypersensitivity. Local inflammatory reactions after intramuscular injection of a vitamin A preparation were considered[1] to be due to a hypersensitivity reaction to polysorbate 80, included as an excipient. Anaphylactoid reactions which occurred in 2 patients after treatment with omalizumab for 27 and 13 months respectively, were likely to be due to the polysorbate excipient and not to the monoclonal antibody itself.[2] The presence of polysorbate 80 in the injection may also contribute to hypersensitivity reactions to docetaxel (see Adverse Effects of Docetaxel, p. 781.3).

1. Shelley WB, *et al.* Polysorbate 80 hypersensitivity. *Lancet* 1995; 345: 1312–13.
2. Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007; 28: 313–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sinroncar; *Belg.*: Oleosorbate†; *Canad.*: Dioptears; *Fr.*: Cerumenol†; *USA*: OptiZen; Viva-Drops.

Multi-ingredient Preparations. *Arg.*: Endura; Otoclean Gotas Oticas; *Fin.*: Expigen; *Fr.*: Fluisedal sans promethazine; Fluisedal; Paroplak†; Prorhinel; *Hong Kong*: Asonor; *S.Afr.*: Expigen; *Singapore*: Endura; *Switz.*: Prorhinel; Rhinocure simplex; Rhinocure; *Thai.*: Endura; *Turk.*: Kansilak; Libalaks; *UK*: Asonor; Episil; *USA*: Episil; Refresh Dry Eye Therapy; Soothe XP; Soothe.

Polyvinyl Acetate

Acetato de polivinilo; Poli(octan winylu); Poli(vinil-acetát); Polivinilacetatas; Polivinüülatsetaat; Poly(acétate de vinyle); Polyvinylacetaat; Polyvinylacetat; Poly(vinylacetat); Polyvinylacetát; Poly(vinylis Acetas); Polyvinylis Acetas; Poly(vinyyliasetaatti); Поливинилацетат.

CAS — 9003-20-7.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF Eur.* also includes a 30% dispersion and *USNF* a 25 to 30% dispersion.

Ph. Eur. 8: (Poly(vinyl acetate)). A white or almost white powder or colourless granules or beads. Practically insoluble in water; soluble in alcohol; freely soluble in ethyl acetate. It is hygroscopic and swells in water. It softens at temperatures above 40 degrees to 50 degrees. Store in airtight containers.

Ph. Eur. 8: (Poly(Vinyl Acetate) Dispersion 30 per cent). A dispersion in water of polyvinyl acetate having a mean relative molecular mass of about 450 000. It may contain povidone and a suitable surface-active agent, such as sodium laurilsulfate, as stabilisers.

An opaque, white or almost white, slightly viscous liquid. Miscible with water and with alcohol. It is sensitive to spoilage by microbial contaminants. Store at a temperature of 5 degrees to 30 degrees.

USNF 31: (Polyvinyl Acetate). A white or off-white powder or colorless granules or beads. It is hygroscopic and swells in water. Practically insoluble in water; soluble in alcohol, in acetone, and in chloroform; freely soluble in ethyl acetate.

USNF 31: (Polyvinyl Acetate Dispersion). It contains 25 to 30% of polyvinyl acetate. It may contain suitable surface active agents and stabilisers. An opaque, white or off-white, slightly viscous liquid. Miscible with water and with alcohol. pH 3.0 to 5.5. Store in airtight containers at a temperature below 25 degrees. Protect from freezing.

Polyvinyl Acetate Phthalate

Polivinilo, acetato ftalato de; Поливинилацетата Фталат.

UNII — 58QVG85GW3.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyvinyl Acetate Phthalate). A reaction product of phthalic anhydride and a partially hydrolysed polyvinyl acetate. It contains 55.0 to 62.0% of phthalyl groups, calculated on an anhydrous acid-free basis. It is a free-flowing white powder that may have a slight odour of acetic acid. Insoluble in water, in chloroform, and in dichloromethane; soluble in alcohol and in methyl alcohol. Store in airtight containers.

Profile

Polyvinyl acetate phthalate is a viscosity-modifying agent that is used in the manufacture of enteric coatings for tablets. Polyvinyl acetate is used in tablet coating; it is also widely used as a glue.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Fittydent.

Polyvinyl Alcohol

Alcohol polivinílico; Alcohol Polyvinylicus; Alcool polivinilico; Alcool polyvinylique; Alkohol poliwinylowy; Polivinil Alkol; Poli(vinil-alkohol); Polivinilo alkoholis; Poly(alcohol Vinylicus); Poly(alcool vinylique); Polyvinylalcohol; Poly(vinylalkohol); Polyvinylalkohol; Poly(vinyylialkoholi); Поливиниловы Спирт.

CAS — 9002-89-5.

UNII — 532B59J990.

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

Ph. Eur. 8: (Poly(Vinyl Alcohol)). It is obtained by polymerisation of vinyl acetate followed by partial or complete hydrolysis of polyvinyl acetate in the presence of catalytic amounts of alkali or mineral acids. Various grades are available and they differ in their degree of polymerisation and their degree of hydrolysis, which determine the physical properties of the different grades. They are characterised by the viscosity and the ester value of the substance. The mean relative molecular mass lies between 20 000 and 150 000. The viscosity is 3 to 70 millipascal seconds. The ester value, which characterises the degree of hydrolysis, is not greater than 280.

Polyvinyl alcohol occurs as a yellowish-white powder or translucent granules. Soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 4% solution in water has a pH of 4.5 to 6.5.

USP 36: (Polyvinyl Alcohol). A synthetic resin represented by the formula $(CH_2CHOH)_n$, where the average value of n is 500 to 5000. It is prepared by 85 to 89% hydrolysis of polyvinyl acetate. White to cream-coloured, odourless, granules or powder. Freely soluble in water at room temperature; solution may be effected more rapidly at somewhat higher temperatures. pH of a 4% solution in water is between 5.0 and 8.0. Store in a dry place.

Profile

Polyvinyl alcohol is a nonionic surfactant (p. 2164.2) that is used in pharmaceutical manufacturing as a stabilising agent and as a viscosity-increasing agent and lubricant.

Polyvinyl alcohol has also been used in the preparation of jellies that dry rapidly when applied to the skin to form a soluble plastic film.

Polyvinyl alcohols of various grades are used for a wide variety of industrial applications.

Polyvinyl alcohol has been used to increase the viscosity of ophthalmic preparations thus prolonging contact of the active ingredient with the eye. It is included in artificial tears preparations used for dry eye (p. 2190.1) and in contact lens solutions (p. 1730.2). For dry eye it is often used in a concentration of 1.4% with or without povidone.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bio Tears; Lagrima Artificial; Lentisol†; Lersan Lagrimas; Liquifilm Lagrimas; Natura Wet; Total Solucion†; *Austral.*: Liquifilm; PVA; *Belg.*: Liquifilm; *Braz.*: Lacril; *Canad.*: Artificial Tears; Hypotears; Liquifilm†; Optilube PVA; *Chile*: Lagrimas Artificiales; Visidic; *Denm.*: Lacril; *Fin.*: Liquifilm; Oftan†; *Ger.*: Liquifilm; Vistil; *Gr.*: Liquifilm Tears; *Hong Kong*: Liquifilm; PMS-Artificial Tears†; *Hung.*: Humalac A and C; *India*: Alphagan; Liquifilm Tears; *Indon.*: Optifresh†; *Irl.*: Liquifilm; Sno Tears†; *Israel*: Liquifilm Tears; *Ital.*: Lacrilux; Vistil; *Malaysia*: Liquifilm; *Mex.*: Acuafil Ofteno; Lubrik; *Norw.*: Kunstig Tarevaesket; Ocufri†; *NZ*: Liquifilm; *Pol.*: Lacrimal; *Port.*: Liquifilm; *S.Afr.*: Liquifilm Tears†; *Singapore*: Hypotears; Liquifilm Tears; *Spain*: Liquifilm Lagrimas; *Swed.*: Sincon; *Switz.*: Liquitears; *Thai.*: Liquifilm Tears; *Turk.*: Liquifilm; *UK*: Liquifilm Tears; Refresh; Sno Tears; *USA*: Akwa Tears; Dry Eyes; Liquifilm†; Nu-Tears; Ocu-Tears; Puralube; Tears Again; *Venez.*: Acuafil Ofteno; Lacril.

Multi-ingredient Preparations. *Arg.*: Consil†; Latlas Fresh; Latlas; Panoptic Lagrimas; Soquette†; *Austral.*: Murine Revital Eyes; Murine Tears†; Refresh; *Austria*: Siccaprotect; *Braz.*: Fresh Clear; Refresh; *Canad.*: Artificial Tears Extra; Artificial Tears Plus; Clear Eyes Triple; Murine; Refresh; Tears Plus; *Chile*: Red Off Aqua; *Cz.*: Siccaprotect; *Fr.*: Refresh; *Ger.*: Dispatenol; Lacrimal OK; Liquifilm OK; Siccaprotect; *Gr.*: Onufrid; Refresh; *Hong Kong*: Hypotears; Murine Natural Tears†; Murine Plus Natural†; *India*: Aansoo; Adle; Aquatears; Dudrop; Eyedrip; Flotears; I-Lube; Irisol Plus; Lacrisan; Lacrisol; Mist; Moss Eye; Ocuwet; Optilube; *Irl.*: Refresh; *Israel*: Refresh; *Ital.*: Hypotears; *Malaysia*: Hypotears; *Mex.*: Lagrifilm Plus; Solrictor con Lagrifilm; *Neth.*: Tears Plus†; *NZ*: Refresh; *Rus.*: Ophtholique (Офтолик); *S.Afr.*: Refresh; Tears Plus†; *Singapore*: Bio-Taches Masque†; Murine Plus; Refresh; *Spain*: Liquifresh; *Switz.*: Hypotears; Siccaprotect; *Thai.*: Refresh; *Turk.*: Refresh; Siccaprotect; *UK*: Blink; *Ukr.*: Ophtholique (Офтолик); *USA*: Preshkote; Hypotears; Murine Plus; Murine†; Nu-Tears II; Refresh Classic; Refresh Redness Relief; Tears Plus.

Ponceau 4R

Brilliant Ponceau 4RC; Brilliant Scarlet; CI Food Red 7; Coccine Nouvelle; Cochenillerot A; Cochineal Red A; Colour Index No. 16255; Czerwień Koszenilowa A; E124; Nykockin; Punzó 4R; Rojo de Cochinilla A; Rouge Cochenille A; Uuskokkiinl; Понсо 4R; Пунцовый 4R.

Trisodium 7-hydroxy-8-(4-sulphonato-1-naphthylazo)-naphthalene-1,3-disulphonate.

$C_{20}H_{11}N_2Na_3O_{10}S_3$=604.5

CAS — 2611-82-7.

UNII — Z525CBK9PG.

Profile

Ponceau 4R is a synthetic azo dye used as a colouring agent in medicines, cosmetics, and foods. Sensitivity reactions have been reported.

Potassium Metaphosphate

E452 (potassium polyphosphates); Polifosfato potásico; Potassium Kurrol's Salt; Potassium Polymetaphosphate; Метафосфорнокислый Калий; Метафосфат Калия.

$(KPO_3)_x$

CAS — 7790-53-6.

UNII — 01DMT14Z63.

Pharmacopoeias. In *USNF.*

USNF 31: (Potassium Metaphosphate). A straight-chain polyphosphate, having a high degree of polymerisation. It contains the equivalent of 59 to 61% of P_2O_5. A white, odourless powder. Insoluble in water; soluble in dilute solutions of sodium salts.

Profile

Potassium metaphosphate is used as a buffer.

Povidone *(BAN, USAN, rINN)*

E1201; Polivinilpirolidon; Polivinilpirolidons; Polivinilpirrolidona; Polivinilpirrolidone; Poliwinylopirolidon; Polyvidone; Polyvidonum; Polyvinylpyrrolidon; Polyvinylpyrrolidone; Povidon; Povidona; Povidonas; Povidoni; Povidonum; Powidon; PVP; Vinylpyrrolidinone Polymer; Повидон.

Poly (2-oxopyrrolidin-1-ylethylene).

$(C_6H_9NO)_n$

CAS — 9003-39-8.

UNII — FZ989GH94E.

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

Ph. Eur. 8: (Povidone). Linear polymers of 1-ethenylpyrrolidin-2-one. The different types of povidone are char-

acterised by their viscosity in solution. A white or yellowish-white, hygroscopic powder or flakes. Freely soluble in water, in alcohol, and in methyl alcohol; very slightly soluble in acetone. A 5% solution in water has a pH of 3.0 to 7.0 depending on the viscosity. Store in airtight containers.

USP 36: (Povidone). A synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerisation of which results in polymers of various molecular weights. The different types of povidone are characterised by their viscosity in aqueous solution, relative to that of water, expressed as a K-value. A white to slightly creamy-white, hygroscopic powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in acetone; practically insoluble in ether. pH of a 5% solution in water is between 3.0 and 7.0 (depending on K-values). Store in airtight containers.

Copovidone

Copolyvidonet; Copolyvidonum; Copovidon; Copovidona; Copovidonum; Kopovidon; Kopovidonas; Kopovidoni; Коповидон.

CAS — 25086-89-9.
UNII — D9C330MD8B.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Copovidone). A copolymer of 1-vinylpyrrolidin-2-one and vinyl acetate in the mass proportion 3:2. A white or yellowish-white, hygroscopic powder or flakes. Freely soluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

USNF 31: (Copovidone). A copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a mass proportion of 3:2. A white to yellowish-white, hygroscopic, powder or flakes. Freely soluble in water, in alcohol, and in dichloromethane; practically insoluble in ether. Store in airtight containers.

Crospovidone (BAN, rINN)

Crospovidon; Crospovidona; Crospovidonum; Krospovidon; Krospovidonas; Krospovidoni; Kroszpovidon; Polyplasdone XL; Кросповидон.

CAS — 9003-39-8.
ATC — A07BC03.
ATC Vet — QA07BC03.
UNII — 68401960MK.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Crospovidone). A cross-linked homopolymer of 1-ethenylpyrrolidin-2-one. Two types of crospovidone are available, depending on the particle size: type A and type B. A white or yellowish-white, hygroscopic powder or flakes. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from moisture.

USNF 31: (Crospovidone). A synthetic cross-linked homopolymer of *N*-vinyl-2-pyrrolidinone. A white to creamy-white, hygroscopic powder having a faint odour. Insoluble in water and in ordinary organic solvents. pH of a 1% suspension in water is between 5.0 and 8.0. Store in airtight containers.

Uses and Administration

Povidone is used in pharmaceutical manufacturing as a suspending and dispersing agent and as a tablet binding, granulating, and coating agent. It is used as a carrier for iodine (see Povidone-Iodine, p. 1767.1). An insoluble cross-linked form of povidone known as crospovidone is used as a tablet disintegrant. Copovidone, a copolymer with vinyl acetate, is used as a tablet binding and coating agent.

Povidone is included in artificial tears preparations used in the management of dry eye (p. 2190.1) and in solutions for contact lens care (p. 1730.2). For dry eye it is often used in a concentration of 0.6% with other viscosity-increasing agents (such as polyvinyl alcohol); it may also be used alone in solutions containing 1.5 to 5%.

Povidone has also been used as an adsorbent in gastrointestinal disorders.

Povidone was formerly used as a plasma expander but other compounds are now preferred.

Adverse Effects

Some products intended for parenteral use contain povidone as an excipient and injection has led to deposition of povidone in the tissues with consequent lesions and pain. There have been occasional reports of liver involvement.

Reviews of adverse effects associated with pharmaceutical excipients including povidone.

1. Golightly LK, *et al.* Pharmaceutical excipients: adverse effects associated with 'inactive ingredients' in drug products (part II). *Med Toxicol* 1988; 3: 209–40.

Hypersensitivity. For reference to anaphylaxis caused by the povidone component of povidone-iodine, see p. 1767.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hypotears Plus; Renu Plus Gotas; Sol-O-Flex†; *Austria*: Oculotect; Protagent; *Belg.*: Oculotect; Siccagent; Telebrix Hystero; *Braz.*: Hypotears Plus; *Chile*: Lepex; Oculotect†; *Cz.*: Arufil; Hypotears Plus; *Denm.*: Oculac; *Fin.*: Oculac; *Fr.*: Dulcilarmes; Fluidabak; Larmecran†; Nutrivisc; Unifluid; *Ger.*: Alodair†; Arufil†; Lacophtal; Lacri-Stulln; Oculotect Fluid; Protagent; Vidisept; Wet-COMOD; *Gr.*: Oculotect; Protagent; *Hong Kong*: Hypotears Plus; Protagent; *Hung.*: Arufil†; Oculotect; *India*: Hypotears Plus; *Irl.*: Oculotect†; *Israel*: Hypotears E; *Ital.*: Clarover; Nu-Gel; Wet-COMOD; *Malaysia*: Oculotect†; *Mex.*: Hypotears Plus; Logical†; Renu Plus†; *Mon.*: Bolinan; *Neth.*: Duratears Free; Oculotect; Protagens; Vidisic PVP; *Norw.*: Oculac; *Philipp.*: Oculotect; Vidisept N; *Pol.*: Oculotect; Vidisept; *Port.*: Oculotect; *Rus.*: Enterodes (Энтеродес); Vid-COMOD (Вид-КОМОД); *S.Afr.*: Hypotears†; *Singapore*: Oculotect; Vidisept N†; *Spain*: Oculotect; *Swed.*: Oculac; *Switz.*: Lacri-Stulln; Oculac; Protagent; *Thai.*: Hypotears Plus†; *Turk.*: Oculotect; Protagent; *UK*: Alodair; Oculotect†; *USA*: Soothe Hydration; *Venez.*: Hypotears Plus.

Multi-ingredient Preparations. *Arg.*: Maxilac†; Panoptic Lagrimas; Visine Plus; *Austral.*: Murine Revital Eyes; Murine Tears†; QV Flare Up; Refresh; Visine Advanced Relief; Visine Professional†; *Braz.*: Refresh; *Canad.*: Artificial Tears Extra; Artificial Tears Plus; Clear Eyes Triple; Murine; Refresh; Tears Plus; Visine Advance Triple Action; *Chile*: Geldair; *Fr.*: Poly-Karaya; Refresh; *Ger.*: Geldair; Lacrimal OK; Lacrisic; Liquifilm OK; Visine Trockene Augen; Visine zur Nacht; *Gr.*: Onufrid; Refresh; *Hong Kong*: Murine Natural Tears†; Murine Plus Natural†; *India*: Aansoo; Adle; Aquatears; Dudrop; Eyedrip; I-Lube; Irisol Plus; Lacrisan; Mist; Moss Eye; Ocuwet; Optilube; *Indon.*: Alodair; *Irl.*: Refresh; *Israel*: Aphtagone†; Aptha-X†; Lacrimol; Refresh; V-Crima; *Ital.*: Filmabak; Visine Dry Eyes†; *Malaysia*: Alodair; *Mex.*: Lagrifilm Plus; Soyaloid; Soydex; Visine Extra; *Neth.*: Tears Plus†; *NZ*: Refresh; Visine Advanced Relief; *Rus.*: Gluconeodesum (Глюконеодез); Haemodez-N (Гемодез-Н); Krashaemodes (Красгемодез); Neohemodes (Неогемодез); Ophthollique (Офтолик); *S.Afr.*: Refresh; Tears Plus†; *Singapore*: Murine Plus; Refresh; *Spain*: Liquifresh; *Thai.*: Refresh; *Turk.*: Refresh; *UK*: Geldair; *Ukr.*: Ophthollique (Офтолик); *USA*: Advanced Relief Visine; Preshkote; Geldair; Murine Plus; Murine†; Refresh Classic; Tears Plus.

Propylene Carbonate

Carbonato de propileno; Пропиленкарбонат.

4-Methyl-1,3-dioxolan-2-one.

$C_4H_6O_3$=102.1

CAS — 108-32-7.
UNII — 8D08K3S51E.

Description. Propylene carbonate is a clear colourless mobile liquid. Freely soluble in water; miscible with alcohol and with chloroform; practically insoluble in petroleum spirit.

Pharmacopoeias. In *USNF.*

USNF 31: (Propylene Carbonate). Sp. gr. 1.203 to 1.210 at 20 degrees. Store in airtight containers.

Profile

Propylene carbonate is used as a solvent in oral and topical pharmaceuticals and for cellulose-based polymers and plasticisers. It has been used as a nonvolatile, stabilising liquid carrier in hard gelatin capsules.

Propylene Glycol

E1520; Glicol Propilênico; Glicole propilenico; Glikol propylenowy; Propilenglicol; Propilénglikol; Propilenglikolis; Propilènglikols; Propilenoglicol; Propüleenglükool; Propyleenglycol; Propyleeniglykoli; Propylèneglycol; Propylenglycol; Propylenglycolum; Propylenglykol; Пропиленгликоль.

(±)-Propane-1,2-diol.

$C_3H_8O_2$=76.10

CAS — 57-55-6 ((±)-propylene glycol); 4254-16-4 ((±)-propylene glycol); 4254-14-2 ((-)-propylene glycol); 4254-15-3 ((+)-propylene glycol).
ATC Vet — QA16QA01.
UNII — 6DC9Q167V3.

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

Ph. Eur. 8: (Propylene Glycol). A clear, colourless, viscous, hygroscopic liquid. Miscible with water and with alcohol. Store in airtight containers.

USP 36: (Propylene Glycol). A clear, colourless, practically odourless, viscous liquid. It absorbs moisture when exposed to moist air. Miscible with water, with acetone, and with chloroform; soluble in ether; will dissolve in many essential oils but is immiscible with fixed oils. Store in airtight containers.

Uses and Administration

Propylene glycol is widely used in pharmaceutical manufacturing as a solvent and vehicle, especially for drugs unstable or insoluble in water. It may also be used as a stabiliser in vitamin preparations, as a plasticiser, and as a preservative. Propylene glycol is used extensively in foods and cosmetics.

Propylene glycol has humectant properties and is used similarly to glycerol in topical moisturising preparations.

Propylene glycol is used in veterinary medicine as a glucose precursor.

Adverse Effects, Treatment, and Precautions

Systemic toxicity of propylene glycol is considered to be low after oral doses unless large quantities have been ingested, or when preparations containing propylene glycol are given to neonates or to patients in renal failure. Systemic toxicity is manifested most commonly by CNS depression, especially in neonates and children. Other reported adverse effects include hepatic or renal impairment, intravascular haemolysis, seizures, hypoglycaemia, coma, arrhythmias, and cardiorespiratory arrest. Hyperosmolality has occurred, particularly in small infants and in patients with renal impairment; lactic acidosis may also be a greater problem in the latter group. Management of toxicity is symptomatic, with appropriate supportive care (see p. 1537.1). In severely poisoned patients who do not respond to supportive management, treatment with alcohol or fomepizole, to inhibit propylene glycol metabolism, may be considered; haemodialysis may also be of use.

After topical use, propylene glycol may produce some local irritation, particularly if applied under occlusive dressings or to mucous membranes; toxicity may occur on application to burns. Hypersensitivity reactions have also been reported. Local sensitivity has been reported after use of ear drops with a propylene glycol vehicle. Injections of preparations containing high concentrations of propylene glycol may produce pain or irritation.

Toxicity. Use of propylene glycol as a solubiliser in parenteral preparations has been suggested as the cause of toxicity in some patients. Hyperosmolality, metabolic acidosis, and nephrotoxicity seen in patients after prolonged or excessive doses of *lorazepam* injection have been attributed to propylene glycol in the formulation;[1-4] the injection also contains macrogol (polyethylene glycol) 400 and this has also been suggested as the cause.[5,6] Most of the reported patients recovered with supportive therapy and haemodialysis,[1,3,5,6] but fatalities also occurred.[2,4] An observational study[7] found that metabolic disturbances were common in patients receiving intravenous *benzodiazepines* formulated with propylene glycol but not in those receiving alternative benzodiazepines; Lactic acidosis has also been reported[8] in a patient who received a high-dose continuous intravenous infusion of a *pentobarbital* formulation containing 40% v/v of propylene glycol; symptoms resolved on stopping therapy.

Propylene glycol and macrogol 400 in enteral solutions of lorazepam and diazepam have also been suggested[9] as the cause of diarrhoea in an infant given large oral doses, possibly due to their combined osmotic effect.

1. Seay RE, *et al.* Possible toxicity from propylene glycol in lorazepam infusion. *Ann Pharmacother* 1997; 31: 647–8. Woycik CL, Walker PC. Correction and comment: possible toxicity from propylene glycol in injectable drug preparations. *ibid.*; 1413.
2. Neale BW, *et al.* Propylene glycol-induced lactic acidosis in a patient with normal renal function: a proposed mechanism and monitoring recommendations. *Ann Pharmacother* 2005; 39: 1732–6.
3. Zar T, *et al.* Acute kidney injury, hyperosmolality and metabolic acidosis associated with lorazepam. *Nat Clin Pract Nephrol* 2007; 3: 515–20.
4. Zosel A, *et al.* Severe lactic acidosis after an iatrogenic propylene glycol overdose. *Pharmacotherapy* 2010; 30: 219.
5. Laine GA, *et al.* Polyethylene glycol nephrotoxicity secondary to prolonged high-dose intravenous lorazepam. *Ann Pharmacother* 1995; 29: 1110–14.
6. Tayar J *et al.* Severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam. *N Engl J Med* 2002; 346: 1253–4.
7. Wilson KC, *et al.* Propylene glycol toxicity: a severe iatrogenic illness in ICU patients receiving IV benzodiazepines: a case series and prospective, observational pilot study. *Chest* 2005; 128: 1674–81.
8. Miller MA, *et al.* Propylene glycol-induced lactic acidosis in a patient receiving continuous infusion pentobarbital. *Ann Pharmacother* 2008; 42: 1502–6.
9. Marshall JD, *et al.* Diarrhea associated with enteral benzodiazepine solutions. *J Pediatr* 1995; 126: 657–9.

Interactions

Anticoagulants. Propylene glycol has been reported to decrease the effect of *heparin.*[1]

1. Col J, *et al.* Propylene glycol-induced heparin resistance during nitroglycerin infusion. *Am Heart J* 1985; 110: 171–3.

Pharmacokinetics

Propylene glycol is rapidly absorbed from the gastrointestinal tract. There is evidence of topical absorption when applied to damaged skin.

It is extensively metabolised in the liver mainly by oxidation to lactic and pyruvic acid and is also excreted in the urine unchanged.

References.
1. Yu DK, *et al.* Pharmacokinetics of propylene glycol in humans during multiple dosing regimens. *J Pharm Sci* 1985; 74: 876–9.
2. Speth PAJ, *et al.* Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. *Ther Drug Monit* 1987; 9: 255–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Advanced Eye Relief; Systane Balance.

Multi-ingredient Preparations. *Arg.*: Punto G†; Systane; *Austral.*: Dermatech Liquid†; Systane; *Braz.*: Mirugell; *Canad.*: Bausch & Lomb Moisture Eyes; Episec; Lubricating Nasal Gel; Lubricating Nasal Mist; Manorapid Synergy; Rhinaris; Salinex Nasal Lubricant; Secaris; Systane; *Chile*: Systane; *China*: Systane (思然); *Fr.*: Intrasite; Propy-Lacticare†; Systane; *Hong Kong*: Moisture Eyes; Systane; *India*: Dew Derm; Diafoot; Emolene; Foot Care; Fungidrops; Gowet; Moisturex-AF; Moisturex; *Indon.*: Sodermix; Systane; *Israel*: Systan UL; Systane; *Ital.*: Cue Soluzione Otologica; Dopo Pik; Sekudrill†; Systane; *Malaysia*: Systane; *Mex.*: Moisture Eyes; Systane; *Philipp.*: Moisture Eyes; Systane; *S.Afr.*: Aserbine; *Singapore*: Effaclar K; Octenisept Wound Gel; Systane; *Spain*: Acerbiol†; *Thai.*: Systane; *Turk.*: Systane; *UK*: Episil; *USA*: Astroglide; Biotene with Calcium; Episil; Sonafine; Surgel; Systane; Zonite; *Venez.*: Systane.

Pharmacopoeial Preparations
BP 2014: Propylene Glycol Solution.

Propylene Glycol Caprylates

Propylene Glycol Dicaprylocaprate

Propilenglikolio dikaprilokapratas; Propyleeniglykolidikaprylokapraatti; Propylene Glycol Octanoatedecanoate; Propylèneglycol, dicaprylocaprate de; Propylenglycoi Octanoas et Decanoas; Propylenglycoldicaprylocaprat; Propylenglycoli Dicaprylocapras; Propylenglycoli Dioctanodidecanoas; Propyleniglykoldikaprylokaprat; Propylenglykol-dioktanodidekanoát.

CAS — 68583-51-7 (propylene glycol dicaprylocaprate); 53824-77-4 (propylene glycol dicaprate); 7384-98-7 (propylene glycol dicaprylate).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Propylene Glycol Dicaprylocaprate). Propylene glycol diesters of saturated fatty acids of vegetable origin, mainly octanoic acid and decanoic acid ($C_{10}H_{20}O_2$). An almost colourless to light yellow, oily liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in fatty oils and in petroleum spirit. Protect from light.

USNF 31: (Propylene Glycol Dicaprylate/Dicaprate). A mixture of the propylene glycol mono-and diesters of octanoic acid and decanoic acid, the diesters fraction being predominant. Clear, colourless or slightly yellow oily liquid at 20 degrees. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in fatty oils and in petroleum spirit. Protect from moisture.

Propylene Glycol Monocaprylate

Propylene glycol mono-octanoate.
CAS — 31565-12-5.

Pharmacopoeias. In *USNF.*

USNF 31: (Propylene Glycol Monocaprylate). A mixture of the propylene glycol monoesters and diesters of fatty acids composed mainly of octanoic acid. Propylene Glycol Monocaprylate Type I contains 55 to 80% of the monoesters and 20 to 45% of the diesters. Propylene Glycol Monocaprylate Type II contains not less than 90% of the monoesters and not more than 10% of the diesters. A clear, colourless, or slightly yellow, oily liquid at 20 degrees. Practically insoluble in water; very soluble in alcohol, in chloroform, and in dichloromethane. Protect from moisture.

Profile

Propylene glycol caprylates are propylene glycol ester nonionic surfactants (p. 2164.2). They are used as oily vehicles and emulsifying and solubilising agents in oral and topical preparations. Both the monocaprylate and mixtures of the dicaprylate and dicaprate (dicaprylocaprate) are used. Propylene glycol dicaprate (propylene glycol didecanoate) has been used similarly.

Propylene Glycol Diacetate

1,2-Diacetoxypropane; Propilenglicol, diacetato de; 1,2-Propylene Diacetate; Диацетат Пропиленгликоля.
1,2-Propanediol diacetate.
$C_7H_{12}O_4$=160.2
CAS — 623-84-7 (1,2-isomer); 628-66-0 (1,3-isomer).
UNII — 5Z492UNF9O.

Profile

Propylene glycol diacetate is a propylene glycol ester nonionic surfactant (p. 2164.2). It is used as an emulsifying and/or solubilising agent, and a solvent. It is included in some external preparations for ear infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *NZ*: VoSol; *USA*: Acetasol HC; Acetasol.

Propylene Glycol Laurates

E477 (propylene glycol esters of fatty acids); Propilenglicol, laurato de; Пропиленгликоля Лаураты.
UNII — 40KT317HGP.

Propylene Glycol Dilaurate

E477 (propylene glycol esters of fatty acids); Propilenglicol, dilaurato de; Propilenglikolio dilauratas; Propyleeniglykolidilauraatti; Propylene Dilaurate; Propylèneglycol, dilaurate de; Propylenglycoldilaurat; Propylenglycoli dilauras; Propylenglykoldilaurat; Propylenglykol-dilaurát; Пропиленгликоля Дилаурат.
CAS — 22788-19-8.
UNII — RMY7XGC3LV.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Propylene Glycol Dilaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains a minimum of 70% of di-esters and a maximum of 30% of mono-esters. The content of free propylene glycol is not more than 2%. A colourless or slightly yellow, clear oily liquid at 20 degrees. Practically insoluble in water; very soluble in alcohol, in methyl alcohol, and in dichloromethane. Protect from moisture.

USNF 31: (Propylene Glycol Dilaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains not less than 70.0% of di-esters and not more than 30.0% of mono-esters. Protect from moisture.

Propylene Glycol Monolaurate

E477 (propylene glycol esters of fatty acids); Propilenglicol, monolaurate de; Propilenglikolio monolauratas; Propyleeniglykolimonolauraatti; Propylèneglycol, monolaurate de; Propylenglycoli monolauras; Propylenglycolmonolaurat; Propylenglykol monolaurát; Propylenglykolmonolaurat; Пропиленгликоля Монолаурат.
CAS — 27194-74-7.
UNII — 668Z5835Z3.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Propylene Glycol Monolaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains 45 to 70% of mono-esters and 30 to 55% of di-esters (type I) or a minimum of 90% of mono-esters and a maximum of 10% of di-esters (type II). The content of free propylene glycol is not more than 5% (type I) or not more than 1% (type II). A colourless or slightly yellow, clear oily liquid at 20 degrees. Practically insoluble in water; very soluble in alcohol, in methyl alcohol, and in dichloromethane. Protect from moisture.

USNF 31: (Propylene Glycol Monolaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains 45 to 70% of mono-esters and 30 to 55% of di-esters (type I) or a minimum of 90% of mono-esters and a maximum of 10% of di-esters (type II). The content of free propylene glycol is not more than 5.0% (type I) or not more than 1.0% (type II). Protect from moisture.

Profile

Propylene glycol mono- and dilaurate are propylene glycol ester nonionic surfactants (p. 2164.2). They are used as emulsifying and solubilising agents, including in food.

Propylene Glycol Monopalmitostearate

E477 (propylene glycol esters of fatty acids); Propilenglicol, monopalmitoestearato de; Propilenglikolio monopalmitostearatas; Propilénglikol-monopalmitil-sztearát; Propyleeniglykolimonopalmitostearaatti; Propyleeniglykolimonostearaatti; Propylene Glycol Monostearate; Propylene Glycol Stearate; Propylèneglycol, monopalmitostéarate de; Propylèneglycol (Stéarate de); Propylenglycoli monopalmitostearas; Propylenglycoli Monostearas; Propylenglycolmonopalmitostearat; Propylenglykolmonopalmitostearát; Propylenglykol-monopalmitostearát; Propylenglykolmonostearat; Prostearin; Пропиленгликоля Монопальмитостеарат.
CAS — 1323-39-3 (propylene glycol monostearate); 29013-28-3 (propylene glycol monopalmitate).
UNII — F76354LMGR (propylene glycol monopalmitostearate); MZM1I680W0 (propylene glycol monostearate).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Propylene Glycol Monopalmitostearate). A mixture of the propylene glycol mono- and di-esters of stearic and palmitic acids. It contains a minimum of 50% of mono-esters produced from the condensation of propylene glycol and stearic acid 50. A white or almost white, waxy solid. M.p. 33 degrees to 40 degrees. Practically insoluble in water; soluble in hot alcohol and in acetone. Protect from light.

USNF 31: (Propylene Glycol Monostearate). A mixture of the propylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 90% of mono-esters of saturated fatty acids, chiefly propylene glycol monostearate and propylene glycol monopalmitate. A white, wax-like solid, beads, or flakes, with a slight agreeable fatty odour. Congealing temperature not less than 45 degrees. Insoluble in water but it may be dispersed in hot water with the aid of a small amount of soap or other suitable surfactant; soluble in organic solvents such as alcohol, acetone, ether, benzene, and fixed or mineral oils.

Profile

Propylene glycol monopalmitostearate is a propylene glycol ester nonionic surfactant (p. 2164.2). It is used as a stabiliser or emulsifier similarly to glyceryl monostearate (p. 2187.2). Self-emulsifying forms are also used.

Pullulan

E1204; Pullulane; Pululano; Пуллулан.
$(C_{36}H_{60}O_{30})_n$
CAS — 9057-02-7.
UNII — 8ZQ0AYU1TT.

Pharmacopoeias. In *Jpn.* Also in *USNF.*

USNF 31: (Pullulan). A neutral, simple polysaccharide produced by the growth of *Aureobasidium pullulans*. It has a chain structure of repeated α-1,6-bonds of maltotriose composed of three glucoses in α-1,4-bonds. It may contain some maltotetraosyl units. It contains not less than 90% of glucan, calculated with reference to the dried substance. A white powder. Freely soluble in water; practically insoluble in dehydrated alcohol.

Profile

Pullulan is a naturally-occurring polysaccharide with adhesive, film-forming, and fibre-forming properties. It is used for tablet coating, as an excipient to aid tabletting processes, in the production of edible films, and as an alternative to gelatin in capsule production. It is also used in the food and cosmetics industries.

References.
1. Leathers TD. Biotechnological production and applications of pullulan. *Appl Microbiol Biotechnol* 2003; 62: 468–73.

Pyrrolidone

2-Pirolidon; Pyrrolidon; 2-Pyrrolidone; Пирролидон.
2-Pyrrolidinone.
C_4H_7NO=85.11
CAS — 616-45-5.
UNII — KKLSD39EOL.

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

Ph. Eur. 8: (Pyrrolidone). A clear, colourless or slightly greyish liquid, or white or almost white crystals, or colourless crystal needles. Miscible with water, with alcohol, and with most common organic solvents. Protect from light.

N-Methylpyrrolidone

Methylpyrrolidon; *N*-Methyl-2-pyrrolidone; *N*-Methylpyrrolidone; Methylpyrrolidonum; *N*-Methylpyrrolidonum; *N*-Metilpirolidonas; *N*-Metylpyrrolidon; *N*-Metylpyrrolidoni; N-Метилпирролидон.

1-Methylpyrrolidin-2-one.
C_5H_9NO=99.13
CAS — 872-50-4.
UNII — JR9CE63FPM.

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

Ph. Eur. 8: (*N*-Methylpyrrolidone). A clear, colourless liquid. Miscible with water and with alcohol. Protect from light.

USP 36: (Methylpyrrolidone). A clear, colourless liquid. Miscible with water and with most organic solvents including alcohol, ketones, and aromatic and chlorinated hydrocarbons. Protect from light.

Profile

Pyrrolidones such as pyrrolidone and *N*-methylpyrrolidone are used as solvents in veterinary formulations and as skin penetration enhancers.

Quillaia

Corteza de Panamá; Corteza de quillay; Corteza palo de jabón; E999 (quillaia extract); Panama Wood; Quilaya; Quillaia Bark; Quillajae Cortex; Quillay; Quillaya, écorce de; Seifenrinde; Soap Bark; Кора Мыльного Дерева.
CAS — 631-01-8 (quillaic acid).
ATC Herb — HR05WA5050 (Quillaja saponaria: bark).
UNII — 8N0K38072W (Quillaja saponaria bark).

Pharmacopoeias. In *Br., Fr.,* and *Swiss. Eur.* (see p. vii) includes Quillaia Bark.

Ph. Eur. 8: (Quillaia Bark; Quillajae Cortex). The whole or fragmented, dried bark, with the cork and underlying parenchyma removed, of *Quillaja saponaria*. It contains not less than 6.5% of triterpene glycosides, expressed as quillaia saponin III, ($C_{104}H_{168}O_{55}$ = 2298), calculated with reference to the dried drug.

BP 2014: (Quillaia). The dried inner part of the bark of *Quillaja saponaria* and other species of *Quillaja* containing not less than 22% of alcohol (45%)-soluble extractive. It is odourless or almost odourless, but the dust or powder is strongly sternutatory.

Uses

Quillaia contains 2 amorphous saponin glycosides, quillaic acid and quillaiasapotoxin. It is used as an emulsifying agent and frothing agent, including in foodstuffs; it is often used with tragacanth mucilage or another thickening agent. Quillaia is also used for its surfactant properties in preparations for skin and respiratory-tract disorders.

Adverse Effects

Quillaia taken orally has been reported to produce gastrointestinal irritation. It has been suggested that the ingestion of large amounts may produce liver damage, respiratory failure, convulsions, and coma.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Fitotos; *Fin.*: Kvilla; *Rus.*: Solutan (Солутан)†; *Spain*: Novogumil; *Swed.*: Quilla simplex.

Pharmacopoeial Preparations
BP 2014: Quillaia Liquid Extract; Quillaia Tincture.

Quinoline Yellow

Amarillo de quinoleína; Canary Yellow; Chinolinegeel; Chinolingelb; Chinolino geltonasis; CI Acid Yellow 3; CI Food Yellow 13; Colour Index No. 47005; E104; Jaune de Quinoléine; Kinolin Sarisi; Kinolingult; Kinolinsárga; Żółcień chinolinowa; Желтый Хинолиновый.
It consists of sodium salts of a mixture of disulfonates (mainly), monosulfonates, and trisulfonates of 2-(2-quinolyl)-1,3-indandione or a mixture containing about two-thirds of 2-(2-quinolyl)-1,3-indandione and one-third of 2-[2-(6-methyl-quinolyl)]1,3-indandione.
CAS — 8004-92-0 (unmethylated disulfonic acids).
UNII — 35SW5USQ3G.

NOTE. D & C yellow No. 10 has been used as a synonym for quinoline yellow, but describes a mixture consisting mainly of a monosulfonate.

Uses

Quinoline yellow is a synthetic dye used as a colouring agent in medicines, cosmetics, and foodstuffs.

Adverse Effects

Hypersensitivity. Hypersensitivity reactions, including a case of severe urticaria,[1] have been attributed to quinoline yellow. Urticarial reactions have also been reported with D & C yellow No.10, a closely related compound.[2]

1. Bell T. Colourants and drug reactions. *Lancet* 1991; 338: 55–6.
2. Gidseg G. Methyldopa-induced skin rash. *South Med J* 1986; 79: 389.

Raspberry

Ahududu; Aviete; Bringebær; Framboesa; Framboise; Framboos; Frambuesa; Fructus Rubi Idaei; Gerd; Hallon; Himbeere; Hindbær; Lampone; Malina; Málna; Vaarikas; Vadelma; Zmeur; Малина.
CAS — 8027-46-1.
UNII — 4N14V5R27W.

Profile

Raspberry, the fresh ripe fruit of *Rubus idaeus* (Rosaceae), is used as a colouring and flavouring agent in medicines and foodstuffs.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: IgeE†; Pruriced; *Indon.*: Proview; *USA*: Immunicare.

Red Cherry

Amareno; Cerasus; Cerise Rouge; Guinda; Hapankirsikka; Kirsebær; Meggy; Paprastoji Vyšnia; Rojo cereza; Sauerkirsche; Sour Cherry; Sur-Kirsebær; Surkörsbär; Tart Cherry; Vişin; Vişne; Višeň; Wiśnia Pospolita; Zure Kers; Вина; Вишня Кислая.
UNII — 9PLM3OM8VL (Prunus avium); 3GH35I9L1L (Prunus cerasus); 1L29G6428X (Prunus cerasus: fruit); 4XTO10247Y (Prunus cerasus fruit juice).

Pharmacopoeias. *USNF* includes cherry juice.

Fr. includes, under the title Griottier, cherry stalks from either the red (sour) cherry, *Prunus cerasus*, or from the sweet cherry, *P. avium*.

USNF 31: (Cherry Juice). The liquid expressed from the fresh ripe fruit of *Prunus cerasus* (Rosaceae). It contains not less than 1.0% of malic acid. pH 3.0 to 4.0. Store in airtight containers. Protect from light.

Profile

Red cherry is used as a colouring and flavouring agent. Cherry stalks (cherry tails) from either red cherry or sweet cherry have been used in herbal medicines. Red cherry juice is under investigation for its antoxidant and anti-inflammatory effects (see below).

Inflammation. Red cherry juice contains anthocyanins and flavonoids and it has been suggested that these may provide antoxidant and anti-inflammatory effects. Small placebo-controlled crossover studies[1,2] have indicated that prior consumption of red cherry juice reduced some symptoms of muscle damage (pain and strength loss) induced by exercise, while another study[3] found that red cherry juice reduced markers of damage after experimentally-induced oxidative stress.

1. Connolly DAJ, *et al.* Efficacy of a tart cherry juice blend in preventing the symptoms of muscle damage. *Br J Sports Med* 2006; 40: 679–83.
2. Kuehl KS, *et al.* Efficacy of tart cherry juice in reducing muscle pain during running: a randomized controlled trial. *J Int Soc Sports Nutr* 2010: 7: 17.
3. Traustadóttir T, *et al.* Tart cherry juice decreases oxidative stress in healthy older men and women. *J Nutr* 2009; 139: 1896–1900.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Vitamina C-Complex; *Fr.*: Evacrine; Hydracur; *Switz.*: Resiston.

Pharmacopoeial Preparations
USNF 31: Cherry Syrup.

Red 2G

Acid Red 1; Azogeranina; Azogeranine; CI Food Red 10; Colour Index No. 18050; E128; Ext. D & C Red No. 11; Geranine 2G; Rojo 2G; Rouge 2G; Красный 2G.
Disodium 5-acetamido-4-hydroxy-3-phenylazonaphthalene-2,7-disulphonate.
$C_{18}H_{13}N_3Na_2O_8S_2$=509.4
CAS — 3734-67-6.

Profile

Red 2G is a synthetic azo dye that may be used as a colouring agent in cosmetics. Its use as a food colour was suspended in the EU in 2007 on the basis that its main metabolite, aniline, has both genotoxic and carcinogenic effects in *rodents*.

Red-Poppy Petal

Rhoead. Pet.; Aguonų birulių žiedai; Coquelicot; Coquelicot, pétales de; Corn Poppy Petal; Klatschrose; Kornvallmokronblad; Květ máku vlčího; Papaveris Rhoeados Flos; Pétalos de Amapola; Rhoeados Petalum; Unikonkukan terälehdet; Мака Самосейки Лепестки.
ATC Herb — HN05CM5018 (Papaver rhoeas: flower); HR05DB5009 (Papaver rhoeas: flower); HN02BG5011 (Papaver rhoeas: flower).
UNII — 9UBF401EYA (Papaver rhoeas); Y1MLS7E68X (Papaver rhoeas: flower); BYL35G8DGJ (Papaver rhoeas: petal); 7J7P659L0Q (Papaver rhoeas seed).

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

Ph. Eur. 8: (Red Poppy Petals). The dried, whole or fragmented petals of *Papaver rhoeas*.

Profile

Red-poppy petal has been used as a colouring agent. It is also included in several herbal preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Formula T13 Tea†; *Fr.*: Calmotisan†; Dystolise; Nocvalene†; *Ital.*: Alruss; Gastrotuss; *Switz.*: Baume Zeller; Pommade au Baume; Tisane pectorale et antitussive.

Red-Rose Petal

Fleur de Rose; Flos Rosae; Pétalos de rosa; Red Rose Petals; Ros. Pet.; Rosae Gallicae Petala; Rosae Petalum; Rose Rouge; Rosenblüte; Лепестки Розы.
ATC Herb — HA01WX5002 (Rosa gallica: flower).
UNII — X8W61WUV70 (Rosa gallica flower).

Pharmacopoeias. In *Fr.*

Profile

Red-rose petal, the petals of the red or Provins rose, *Rosa gallica* (Rosaceae), has been used as a colouring agent and for its mild astringent properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Expectosan Hierbas y Miel.

Homoeopathic Preparations. *Fr.*: Poconeol no 18.

Saccharin

Benzoic Acid Sulphimide; Benzoic Sulfimide; Benzosulphimide; E954; Gluside; Sacarina; Saccarina; Saccharine; Saccharinum; Sacharin; Sacharinas; Sacharine; Sacharyna; Sackarin; Saharin; Sakkariini; Sakkarin; *o*-Sulfobenzimide; Szacharin; Zaharină; Захарин; Сахарин.
1,2-Benzisothiazolin-3-one 1,1-dioxide.
$C_7H_5NO_3S$=183.2
CAS — 81-07-2.
UNII — FST467XS7D.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Saccharin). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in cold water; sparingly soluble in boiling water and in alcohol. It dissolves in dilute solutions of alkali hydroxides and carbonates. A saturated solution, prepared without heating, is acid to litmus.

USNF 31: (Saccharin). White crystals or white, crystalline powder. Is odourless or has a faint, aromatic odour. In dilute solutions, it is intensely sweet. Soluble 1 in 290 of water, 1 in 25 of boiling water, and 1 in 31 of alcohol; slightly soluble in chloroform and in ether; is readily dissolved by dilute solutions of ammonia, by solutions of alkali hydroxides, and by solutions of alkali carbonates with the evolution of carbon dioxide. Its solutions are acid to litmus.

Saccharin Calcium

Benzosulfimida cálcica; Calcium Benzosulphimide; Calcium Saccharin; E954; Sacarina cálcica; Saccharine calcique; Saccharinum calcicum; Кальция Сахарат.

$C_{14}H_8CaN_2O_6S_2.3½H_2O$=467.5

CAS — 6485-34-3 (anhydrous saccharin calcium); 6381-91-5 (hydrated saccharin calcium).

UNII — 09AW1ODN7B (anhydrous saccharin calcium); 5101OP7P2I (hydrated saccharin calcium).

Pharmacopoeias. In *US.*

USP 36: (Saccharin Calcium). White crystals or white, crystalline powder. Is odourless, or has a faint, aromatic odour, and has an intensely sweet taste, even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. Soluble 1 in 2.6 of water and 1 in 4.7 of alcohol.

Saccharin Potassium

E954; Potassium Benzosulphimide; Potassium Saccharate; Potassium Saccharin; Калия Сахарат.

$C_7H_5NO_3SK$=222.3

CAS — 10332-51-1.

UNII — K2BEG3J28N.

NOTE. Although the name Potassium Saccharate has been applied to saccharin potassium do not confuse with Potassium Glucarate, the potassium salt of saccharic acid, which may also be named potassium saccharate.

Saccharin Sodium

Benzosulfimida sódica; E954; Sacarina sódica; Saccharin-Natrium; Saccharin Sod.; Saccharine sodique; Saccharinnatrium; Saccharinum Natricum; Saccharoidum Natricum; Sacharin sodná sůl; Sacharino natrio druska; Sacharyna sodowa; Sackarinnatrium; Sakkariininatrium; Sodium Benzosulphimide; Sodium Saccharin; Soluble Gluside; Soluble Saccharin; Szacharin-nátrium; Натрия Сахарат.

$C_7H_4NNaO_3S$=205.2

CAS — 128-44-9 (anhydrous saccharin sodium); 6155-57-3 (saccharin sodium dihydrate).

UNII — SB8ZUX40TY (saccharin sodium); I4807BK602 (anhydrous saccharin sodium).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn,* and *US.* Some pharmacopoeias specify the dihydrate but it may contain a variable quantity of water as a result of efflorescence.

Ph. Eur. 8: (Saccharin Sodium). A white or almost white, crystalline powder or colourless crystals. It may contain a variable quantity of water. Efflorescent in dry air. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

USP 36: (Saccharin Sodium). White crystals or white, crystalline powder. Is odourless, or has a faint, aromatic odour, and has an intensely sweet taste, even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. When in powdered form, it usually contains about one-third the theoretical amount of water of hydration as a result of efflorescence. Soluble 1 in 1.5 of water and 1 in 50 of alcohol.

Uses and Administration

Saccharin and its salts are intense sweeteners, dilute solutions having about 300 times the sweetening power of sucrose. They are used in pharmaceuticals and in foods and beverages and are heat stable. They have no food value. The salts are more often used than saccharin itself as they are considered to be more palatable.

Adverse Effects

There have been rare reports of hypersensitivity and photosensitivity reactions with saccharin.

Saccharin-associated bladder tumours in *rats* given high doses have been the cause of much concern and investigation. However, it is now generally accepted that these findings are not relevant to the use of saccharin as a sweetener in man.

Effects on the liver. Elevated liver enzyme values in an elderly woman followed use of two different medications sweetened with saccharin sodium.[1] Findings resolved on stopping all preparations containing saccharin, and recurred on rechallenge with a small amount of saccharin sodium.

1. Negro F, *et al.* Hepatotoxicity of saccharin. *N Engl J Med* 1994; 331: 134–5.

Pharmacokinetics

Saccharin is readily absorbed from the gastrointestinal tract. It is almost all excreted unchanged in the urine within 24 to 48 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Dul-Suc; Endulza; Sukar-Sin; ***NZ***: Sactabs; ***Turk.***: Hermesetas; ***Venez.***: Hermesetas.

Multi-ingredient Preparations. ***Arg.***: Chuker; Chuker; Dulsiluet; Kaldil Diet; Rondo; Semble; Sucaryl; Sulmel; ***Austral.***: Sucaryl; ***Braz.***: Finn Cristal; ***Chile***: Endulzante; Sukar-Sin; ***Fr.***: Sucaryl; ***Israel***: Sucrin; ***Ital.***: Diet Sucaryl†; ***NZ***: Sucaryl; ***Rus.***: Zuckli (Цукли)†; ***Thai.***: Corinap; ***Turk.***: Dolce†; Tadalin.

Pharmacopoeial Preparations

USP 36: Saccharin Sodium Oral Solution; Saccharin Sodium Tablets.

Saffron

Açafrão; Azafrán; CI Natural Yellow 6; Colour Index No. 75100; Croci Stigma; Crocus; Estigmas de Azafrán; French Saffron; Keshar; Saffran; Safraan; Safran; Sahrami; Spanish Saffron; Xī Hóng Hhuā; Шафран.

UNII — E849G4X5YJ (Crocus sativus stigma); 00IF91KFKQ (Crocus sativus flower).

NOTE. Do not confuse with the meadow saffron (*Colchicum autumnale*), the source of colchicum (p. 607.1) and colchicine (p. 604.1), or Indian saffron, which is a name sometimes used for Turmeric (p. 2218.1).

Pharmacopoeias. In *Chin.* and *Jpn.*

Eur. (see p. vii) includes Saffron for Homoeopathic Preparations.

Ph. Eur. 8: (Saffron for Homoeopathic Preparations). The dried stigmas of *Crocus sativus* usually joined by the base to a short style. It has a characteristic, aromatic odour. Protect from light.

Profile

Saffron consists of the dried stigmas and tops of the styles of *Crocus sativus* (Iridaceae), containing crocines, crocetins, and picrocrocine. Saffron is used to colour medicines, foods, and cosmetics. It is also used as a flavouring agent. Saffron has been used in herbal and traditional medicines and has been included in preparations for teething pain. It has also been investigated in disorders such as depression and cancer. There have been reports of poisoning with saffron, but in some cases these may have been due to meadow saffron, *Colchicum autumnale*.

Homoeopathy

Saffron has been used in homoeopathic medicines under the following names: Croci stigma; Crocus sativus; Crocus; Croc. s.

References.

1. Schmidt M, *et al.* Saffron in phytotherapy: pharmacology and clinical uses. *Wien Med Wochenschr* 2007; 157: 315–19.
2. Bathaie SZ, Mousavi SZ. New applications and mechanisms of action of saffron and its important ingredients. *Crit Rev Food Sci Nutr* 2010; 50: 761–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Pansoral Primeros Dientes; ***Cz.***: Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; ***Fr.***: Safralite; ***Ger.***: Infi-tract V; ***Hung.***: Bano Svedkeseru; ***India***: Abana; Geriforte; Geriforte; ***Rus.***: Pansoral Teething (Пансорал Первые Зубы); Tentex (Тентекс); ***Singapore***: Tentex Royal; ***Spain***: Dentomicin†; ***Switz.***: Eau pour les yeux†; ***Ukr.***: Imunin (Иммунин)†; Swedish Bitters Dr Theiss (Шведская Др Тайсс)†.

Homoeopathic Preparations. ***Austria***: Orgalem; ***Fr.***: Abbe Chaupitre no 6; Dolirelax†; Sclerocalcine; ***Ger.***: Aderplus spezial Dr Hagedorn†; Cefakliman S; Cimicifuga N Oligoplex; Flenin; Secale-Gastreu.

Shea Butter

Manteca de Karité; Карите; Масло Ши.

UNII — K49155WL9Y (shea butter); O88E196QRF (shea butter extract).

Profile

Shea butter is a natural fat obtained from the kernel of the fruit of *Vitellaria paradoxa* (*Butyrospermum parkii*) (Sapotaceae) indigenous to West Africa. It is used as an ointment and cream basis. Shea butter is widely used in cosmetics. It is also used in cooking oil, and as a substitute for theobroma oil in chocolate manufacturing.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Sigestrial; ***Fr.***: Ictyane HD; Node K; ***Philipp.***: Enfacare; ***Singapore***: Rosken Skin Repair High Potency.

Shellac

E904; Goma laca; Gommalacca; Gomme Laque; Gommes laques; Lacca; Lacca in Tabulis; Schellack; Schellak; Selak; Selakas; Sellak; Shellack; Shellak; Shellakka; Skjellakk; Szelak; Шеллак.

CAS — 9000-59-3.

UNII — 46N107B71O.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Jpn includes Purified Shellac and White Shellac (Bleached).

Ph. Eur. 8: (Shellac). It is obtained by purification of the resinous secretion of the female insect *Kerria lacca* (Kerr) Lindinger (*Laccifer lacca* Kerr). There are 4 types of shellac depending on the nature of the treatment of crude secretion (seedlac): Wax-containing Shellac; Bleached Shellac; Dewaxed Shellac; and Bleached, Dewaxed Shellac.

Brownish-orange or yellow, shining, translucent, hard or brittle more or less thin flakes (Wax-containing Shellac; Dewaxed Shellac), or a creamy-white or brownish-yellow powder (Bleached Shellac; Bleached, Dewaxed Shellac).

Practically insoluble in water. With dehydrated alcohol it gives a more or less opalescent solution (Wax-containing Shellac; Bleached Shellac) or a clear solution (Dewaxed Shellac; Bleached, Dewaxed Shellac). When warmed, it is sparingly soluble or soluble in alkaline solutions. Protect from light. Store Bleached Shellac and Bleached, Dewaxed Shellac at a temperature not exceeding 15 degrees.

USNF 31: (Shellac). It is obtained by purification of lac, the resinous secretion of the insect *Laccifer lacca kerr* (Coccidae). There are 4 varieties: Orange Shellac, Dewaxed Orange Shellac, Regular Bleached (White) Shellac, and Refined Bleached Shellac. Orange Shellac occurs as thin, hard, brittle, transparent, pale lemon-yellow to brownish-orange flakes, having little or no odour. Bleached Shellac occurs as opaque, amorphous, cream to yellow granules or coarse powder, having little or no odour.

Insoluble in water; very slowly soluble in alcohol, 85 to 95% (w/w); soluble in ether, 13 to 15%, in petroleum spirit, 2 to 6%, in benzene, 10 to 20%, and in aqueous solutions of ethanolamines, alkalis, and borax; sparingly soluble in turpentine oil. Store preferably at a temperature not exceeding 8 degrees.

Profile

Shellac is used as an enteric coating for pills and tablets, but disintegration time has been reported to increase markedly on storage.

Preparations

Pharmacopoeial Preparations

USNF 31: Pharmaceutical Glaze.

Silicas

Silice.

Purified Siliceous Earth

Diatomaceous Earth; Diatomeeënaarde; Diatomiet; Diatomita; Diatomitas; Diatomite; Diatomito; Farina fossile; Kremelina; Kieselgur; Kísilgúr; Piimaa; Purified Infusorial Earth; Purified Kieselguhr; Terra Silicea Purificada; Terra de diatomeas; Ziemia okrzemkowa; Очищенный Кремнезём.

CAS — 7631-86-9.

UNII — 2RF6EJ0M85.

Pharmacopoeias. In *USNF.*

USNF 31: (Purified Siliceous Earth). A form of silicon dioxide consisting of frustules and fragments of diatoms purified by calcining. A very fine, white, light grey, or pale buff mixture of amorphous powder and lesser amounts of crystalline polymorphs, including quartz and cristobalite. It is gritty and readily absorbs moisture, and retains about four times its weight of water before becoming fluid. Insoluble in water, in acids, and in dilute solutions of alkali hydroxides.

Silicon Dioxide

Colloidal Hydrated Silica; Ditlenek krzemu; E551; Kiseldioxid, kolloidal, hydratiserad; Koloidinis silicio dioksidas, hidratuotas; Oxid křemičitý koloidní hydratovaný; Piidioksidi, kolloidinen, hydratoitu; Precipitated Silica; Rānidioksīds; Silicija dioksīds; Silica Colloidalis Hydrica; Silica Gel; Silice;

colloidale hydratée; Silice precipitada; Silicio, dióxido de; Siliciumdioxid; Siliciumdioxide; Vizturtalmú, kolloid szilícium-dioxid; Диоксид Кремния; Двуокись Кремния; Силициев диоксид
$SiO_2.xH_2O$=60.08 (anhydrous)
CAS — 63231-67-4; 7631-86-9.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*. *Eur.* and *USNF* also include dental-type silica.

Ph. Eur. 8: (Silica, Colloidal Hydrated). A light, fine, white or almost white, amorphous powder. Practically insoluble in water, and in mineral acids except hydrofluoric acid; dissolves in hot solutions of alkali hydroxides.

Ph. Eur. 8: (Silica, Dental Type). An amorphous silica (precipitated, gel, or obtained by flame hydrolysis). A white or almost white, light, fine amorphous powder. Practically insoluble in water and in mineral acids; dissolves in hydrofluoric acid and in hot solutions of alkali hydroxides.

USNF 31: (Silicon Dioxide). It is obtained by insolubilising the dissolved silica in sodium silicate solution. Where obtained by the addition of sodium silicate to a mineral acid, the product is termed silica gel; where obtained by the destabilisation of a solution of sodium silicate in such a manner as to yield very fine particles, the product is termed precipitated silica. A fine, white, odourless, hygroscopic, amorphous powder in which the diameter of the average particles ranges from 2 to 10 micrometres. Insoluble in water, in alcohol, and in other organic solvents; soluble in hot solutions of alkali hydroxides. pH of 5% slurry in water is between 4.0 and 8.0. Store in airtight containers. Protect from moisture.

USNF 31: (Dental-Type Silica). It is obtained from sodium silicate solution by destabilising with acid in such a way as to yield very fine particles. A fine, white, odourless, hygroscopic, amorphous powder in which the diameter of the average particles ranges from 0.5 to 40 micrometres. Insoluble in water, in alcohol, and in acid (except hydrofluoric acid); soluble in hot solutions of alkali hydroxides. pH of 5% slurry in water is between 4.0 and 8.5. Store in airtight containers.

Colloidal Silicon Dioxide

Acidum Silicicum Colloidale; Colloidal Anhydrous Silica; Colloidal Silica; Hochdisperses Silicumdioxid; Kiseldioxid, kolloidal, vattenfri; Koloidinis silicio dioksidas, bevandenis; Krzemu dwutlenek koloidalny; Oxid křemičitý koloidní bezvodý; Piidioksidi, kolloidinen, vedetön; Silica Colloidalis Anhydrica; Silice colloïdale anhydre; Sílice coloidal; Sílice coloidal anhidra; Silicii Dioxidum Colloidalle; Silicio coloidal, dióxido de; Vízmentes, kolloid, szilícium-dioxid; Коллоидный Диоксид Кремния
SiO_2=60.08
CAS — 7631-86-9.
UNII — ETJ7Z6XBU4.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Eur. and *USNF* also include hydrophobic colloidal silica.

Ph. Eur. 8: (Silica, Colloidal Anhydrous). A light, fine, white or almost white, amorphous powder. It has a particle size of about 15 nm. Practically insoluble in water and in mineral acids except hydrofluoric acid; dissolves in hot solutions of alkali hydroxides. A 3.3% suspension in water has a pH of 3.5 to 5.5.

Ph. Eur. 8: (Silica, Hydrophobic Colloidal; Silica Hydrophobica Colloidalis). Colloidal silicon dioxide partly alkylated for hydrophobation. A light, fine, white or almost white, amorphous powder, not wettable by water. Practically insoluble in water and mineral acids except hydrofluoric acid. It dissolves slowly in hot solutions of alkali hydroxides.

USNF 31: (Colloidal Silicon Dioxide). A submicroscopic fumed silicon dioxide, prepared by the vapour-phase hydrolysis of a silicon compound. A light, white, non-gritty powder of extremely fine particle size (about 15 nm). Insoluble in water and in acid (except hydrofluoric acid); soluble in hot solutions of alkali hydroxides. pH of a 4% dispersion in water is between 3.5 and 5.5.

USNF 31: (Hydrophobic Colloidal Silica). Prepared by partial alkylation for hydrophobation. A light, fine, white or almost white, amorphous powder, not wettable by water. Practically insoluble in water and in mineral acids, except hydrofluoric acid; dissolves slowly in hot solutions of alkali hydroxides.

Uses

Silica is a general name used for the different forms of silicon dioxide. These different forms have various pharmaceutical uses. Purified siliceous earth is used as a filtering medium and adsorbent. Silicon dioxide is used as a suspending and thickening agent and, in the form of silica gel, as a desiccant. Colloidal silicon dioxide is used as a suspending agent and thickener, as a stabiliser in emulsions, and as an anticaking agent and desiccant. Silicon dioxide is also used as an anticaking agent in the food industry.

Silicas and silicic acids have also been used as a source of silicon (p. 2088.3) in dietary supplements.

Homoeopathy

Silicon dioxide has been used in homoeopathic medicines under the following names: Acidum silicicum; Silicea; Sil.

Adverse Effects

Prolonged inhalation of some forms of silica dust may be associated with the development of fibrosis of the lung (silicosis). The forms of silica described here and used as pharmaceutical excipients may cause irritation of the respiratory tract if inhaled but do not appear to be associated with silicosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Celloids S 79†; ***Ger.***: Entero-Teknosal; ***Mon.***: Dissolvurol; ***Rus.***: Polisorb (Полисорб); ***UK***: Aerosil; ***Ukr.***: Gastrogel (Гастрогель)†; Silics (Силикс).

Multi-ingredient Preparations. ***Arg.***: Kelo-Cote; ***Austral.***: Bio-Disc†; Duo Celloids SCP†; Duo Celloids SPS†; Duo Celloids SSS†; Hair Skin & Nails; Nails Hair and Skin; Silica Compound; ***Austria***: Kephalodoron; ***Canad.***: Osteogen; ***Chile***: Cartilago T-500†; Fittig Desodorante; Normaderm Concentrado Activo; Xeragel; ***Fr.***: Gelopectose; Kelo-Cote; Kinesamine; Naturophta Macula; Silibiol; Topaal; Topalkan†; ***Ger.***: anabol-loges†; Aplona; Equisil N†; Kelo-Cote; ***Gr.***: Dyspagone; Gastrovison; ***Hong Kong***: Disflatyl; ***India***: One-Up; Orbone Forte; Orbone; ***Indon.***: Kelo-Cote; ***Irl.***: Topaal; ***Israel***: Adinol†; Kelo-Cote; ***Ital.***: Lacalut; ***Malaysia***: Rowarolan; ***NZ***: Lamisil Odor Eze†; ***Philipp.***: BioSil†; ***S.Afr.***: Lotio Pruni Comp cum Cupro†; Zeel; ***Singapore***: Disflatyl†; Glow; Hair and Nails; ***Switz.***: Acne Creme; Kelo-cote†; ***USA***: NeutraSal.

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox; Elimitona; Hangover Relief; Respatona Nasal Spray Decongestant; Respatona Sinus Relief; Teething Relief; ***Austria***: Nebenhohlen-Tropfen Nr 26†; Osteoplex; Otodolor; Spigelon; Steiroplex; Sulfur Med Complex; Tonsiotren; Zom; ***Canad.***: Calnor†; Combinaison†; Cruroheel S†; Diamite; Earache; Endoteel†; Ervopax†; Formula CA 205†; Homeo-Form P†; Homeo-S-Asp; Hylands Bioplasma; Ikoplex 21†; Ikoplex 5†; Melange†; Minerals+; Nuage Bioplasma†; Optalia†; Phyto-Cal; Rexorubia†; Sinus Ease; Sinuspax†; Spigelon†; Ubicoenzyme; Urticalcin; ***Chile***: Bioactiv D; Bioactiv P; Ikoplex No 15; Ikoplex No 17; Ikoplex No 19; Ikoplex No 1; Ikoplex No 20; Ikoplex No 21; Ikoplex No 23; Ikoplex No 24; Ikoplex No 3; Ikoplex No 4; Ikoplex No 5; Ikoplex No 7; Ikoplex No 8; Ikoplex No 9; Silik; ***Cz.***: Zeel Salbe†; ***Fr.***: Abbe Chaupitre no 23†; Abbe Chaupitre no 48†; Abbe Chaupitre no 79†; Boripharm No 22†; Dermo-Drainol†; Dolirelax†; Jenoverine†; Kreosotum Complexe No 62; Nervopax; Pulmo-Drainol†; Rexorubia; Sclerocalcine; Silicea Complexe No 11; Sinuspax; Veino-Drainol†; ***Ger.***: Araniforce rheuma†; Arthrorell N; Broncho-Injektopas; Derma-Plantin†; Dermarell; Dermi-cyl L Ho-Len-Complex; Disci Bamb; Discocyl Ho-Len-Complex; Drufusan N†; Drufusan; Girheulit HM†; Girheulit HOM; Hevertotox; Hevertotox; Hewelymphon N†; Humoval; Infi-Symphytum; Lymphaden Lymphdrusentabletten; Naranotox comp; Osteoplex; Pascoe-Agil HOM; Pflugerplex Lemna; Ranocalcin HM; Roth's Rotacard; Rufebran rheumo†; Sinuselect N; Sinusitis Hevert SL; Steirocall; Steiroplex†; Tamechol; Tonsillosyx; Tonsiotren H; ***Hung.***: Spigelon; Zeel; ***Neth.***: Chavita I; Geovita; Jenoverine†; Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Lymphomyosot; Nisyspray; Oteel H; Tonsiotreen; ***Rus.***: Pharyngomed (Фарингомед); Tonsilotren (Тонзилотрен); ***Switz.***: Exsepta; Regenaplex Nr. 21c; Regenaplex Nr. 21e; Regenaplex Nr. 24c; Regenaplex Nr. 88b; Sinusin; Sinuspax†; Spigelon; Urticalcin; ***Ukr.***: Tonsilotren (Тонзилотрен).

Silicones

Siliconas; Силиконы.
ATC — A03AX13.
ATC Vet — QA03AX13.

Description. Silicones are polymers with a structure consisting of alternate atoms of silicon and oxygen, with organic groups attached to the silicon atoms. As the degree of polymerisation increases, the products become more viscous and the various grades are distinguished by a number, approximately corresponding to the viscosity of the particular grade. Silicones may be fluids, greases, waxes, resins, or rubbers depending on the degree of polymerisation.

Cyclomethicone

Cyclic Polydimethylsiloxane; Cyclodimethicone; Cyclohexasiloxane (cyclomethicone 6); Cyclopentasiloxane (cyclomethicone 5); Cyclopolydimethylsiloxane; Cyclotetrasiloxane (cyclomethicone 4); Decamethylcyclopentasiloxane (cyclomethicone 5); Dimethylcyclopolysiloxane; Dodecamethylcyclohexasiloxane (cyclomethicone 6); Octamethylcyclotetrasiloxane (cyclomethicone 4); Polydimethylcyclosiloxane; Цикпометикон
$(C_2H_6OSi)_n$
CAS — 69430-24-6 (cyclomethicone); 556-67-2 (cyclomethicone 4); 541-02-6 (cyclomethicone 5); 540-97-6 (cyclomethicone 6).
UNII — NMQ347994Z (cyclomethicone); CZ227117JE (cyclomethicone 4); 0THT5PCI0R (cyclomethicone 5); XHK3U310BA (cyclomethicone 6).

Pharmacopoeias. In *USNF*.

USNF 31: (Cyclomethicone). A fully methylated cyclic siloxane containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, in which *n* is 4, 5, or 6, or a mixture of them. Store in airtight containers and avoid exposure to excessive heat.

Dimeticone *(BAN, rINN)*

Dimethicone (USAN); Dimethyl Silicone Fluid; Dimethylpolysiloxane; Dimethylsiloxane; Dimeticon; Dimeticona; Dimeticonas; Diméticone; Dimeticonum; Dimetikon; Dimetikonas; Dimetikoni; Dimetilpolisiloxano; Dimetykon; E900; Huile de Silicone; Methyl Polysiloxane; Metilpolisiloksan; Metilpolisiloxano; Permethylpolysiloxane; Polidimetilsiloxano; Silicone Oil; Siliconum Liquidum; Диметикон
Poly(dimethylsiloxane).
$CH_3[Si(CH_3)_2O]_nSi(CH_3)_3$
CAS — 9006-65-9.
ATC — A03AX13.
ATC Vet — QA03AX13.
UNII — 92RU3N3Y1O (dimethicone); 2Y53S6ATLU (dimethicone 350); TYU5GP6XGE (dimethicone 410).

Description. Dimeticones are fluid silicones in which the organic group is a methyl radical.

Simeticone (activated dimeticone), a mixture of liquid dimeticones with silicon dioxide, is described on p. 1886.2.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Dimeticone). The degree of polymerisation is such that the kinematic viscosities are nominally between 20 and 1300 mm^2/second; dimeticones with a nominal viscosity of 50 mm^2/second or lower are intended for external use only. Dimeticones are clear, colourless, liquids of various viscosities. Practically insoluble in water; very slightly soluble to practically insoluble in dehydrated alcohol; miscible with ethyl acetate, with methyl ethyl ketone, and with toluene.

USNF 31: (Dimethicone). A mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, stabilised with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3SiO-]$, wherein *n* has an average value such that the corresponding nominal viscosity is in a discrete range between 20 and 30 000 centistokes. It is a clear colourless, odourless liquid. Insoluble in water, in alcohol, in acetone, and in methyl alcohol; very slightly soluble in isopropyl alcohol; soluble in amyl acetate, in chlorinated hydrocarbons, in ether, in *n*-hexane, in petroleum spirit, in benzene, in toluene, and in xylene. Store in airtight containers.

Uses and Administration

Dimeticones and other silicones are water-repellent and have a low surface tension. They are used in topical barrier preparations for protecting the skin against water-soluble irritants. Creams, lotions, and ointments containing a dimeticone are used for the prevention of bedsores and napkin rash and to protect the skin against trauma due to incontinence or stoma discharge. Silicone preparations should not be applied where free drainage is necessary or to inflamed or abraded skin. Silicones, usually a dimeticone, are also used topically as wound dressings, and to reduce scar elevation and pigmentation. They are also used in oral solid dosage forms, including modified-release preparations.

Dimeticones and cyclomethicones are used in the treatment of head pediculosis (p. 2147.3). Solutions containing 4 to 95% dimeticone have been used and act by physically coating the lice and disrupting their water management; cyclomethicones are usually included for their volatility as solvents.

Silicones have also been used for arthroplasty in rheumatic disorders, by intravitreal injection for retinal detachment, and by subcutaneous injection or implantation in reconstructive or cosmetic surgery.

Dimeticones, in particular simeticone (activated dimeticone) (p. 1886.2), are used in the treatment of flatulence.

Pediculosis. References.

1. Burgess IF, *et al.* Treatment of head louse infestation with 4% dimeticone lotion: randomised controlled equivalence trial. *BMJ* 2005; 330: 1423.

2. Burgess IF, *et al.* Randomised, controlled, assessor blind trial comparing 4% dimeticone lotion with 0.5% malathion liquid for head louse infestation. *PLoS One* 2007; 2: e1127.
3. Heukelbach J, *et al.* A highly efficacious pediculicide based on dimeticone: randomized observer blinded comparative trial. *BMC Infect Dis* 2008; 8: 115.
4. Burgess IF. The mode of action of dimeticone 4% lotion against head lice. *Pediculus capitis*. *BMC Pharmacol* 2009; 9: 3.

Retinal detachment. Retinal detachment is separation of the retina from the underlying retinal pigmentary epithelium and usually requires surgical repair. Intravitreal injection of liquid silicone, either alone or with a perfluorocarbon,[1,2] is used for retinal tamponade with or after surgery in complicated or persistent detachment of the retina.[3] In most cases, the silicone fluid is later removed from the eye.[4] High-density silicone fluids are increasingly being used.[5] Use of silicone fluid is reported to trigger a local inflammatory response, which may persist after the fluid is removed.[6] Other late complications after its use may include cataract, glaucoma, and keratopathy.

1. Rizzo S, *et al.* Long-term vitreous replacement with perfluorohexyloctane and silicone oil: preliminary reports of a multicentric study. *Ophthalmologica* 2005; 219: 147–53.
2. Schwartz SG, *et al.* Tamponade in surgery for retinal detachment associated with proliferative vitreoretinopathy. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2009 (accessed 16/06/10).
3. Quiram PA, *et al.* Outcomes of vitrectomy with inferior retinectomy in patients with recurrent rhegmatogenous retinal detachments and proliferative vitreoretinopathy. *Ophthalmology* 2006; 113: 2041–7.
4. Szurman P, *et al.* Primary silicone oil tamponade in the management of severe intraocular foreign body injuries: an 8-year follow-up. *Retina* 2007; 27: 304–11.
5. Herbrig E, *et al.* Anatomical and functional results of endotamponade with heavy silicone oil – Densiron 68 – in complicated retinal detachment. *Ophthalmic Res* 2007; 39: 198–206.
6. Wickham LJ, *et al.* Immunopathology of intraocular silicone oil: retina and epiretinal membranes. *Br J Ophthalmol* 2007; 91: 258–62.

Adverse Effects and Precautions

Adverse effects from the clinical use of silicones appear to be rare. Foreign-body reactions have been reported after their use as joint implants. Other implants, notably breast implants used for reconstruction after mastectomy or for cosmetic purposes, carry the risk of migration of silicone with cyst formation and other complications; accidental intravascular injection has been fatal. Late adverse ocular effects can follow the intravitreal injection of liquid silicone in the management of retinal detachment (see above).

Breast feeding. Concern has been raised regarding the possible effects on infants of mothers with silicone breast implants who breast feed. Oesophageal dysfunction has been reported in several such children,[1] although this finding has not been confirmed by subsequent reports. The last available guidance from the American Academy of Pediatrics therefore stated[2] that the current evidence did not justify classifying silicone implants as a contra-indication to breast feeding.

1. Levine JJ, Ilowite NT. Sclerodermalike esophageal disease in children breast-fed by mothers with silicone breast implants. *JAMA* 1994; 271: 213–6. Correction. *ibid.*: 272: 770.
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 20/11/07)

Connective tissue disorders. Since the introduction of silicone breast implants in the early 1960s there have been many anecdotal reports of connective tissue disorders in women who have undergone breast reconstruction or augmentation with these implants. Scleroderma has been the most frequently reported disorder; others have included SLE, rheumatoid arthritis, and inflammatory myopathies. A syndrome of vague musculoskeletal symptoms, fever, and fatigue has also been reported. These cases led the FDA to call for a moratorium in the USA on the use of silicone breast implants in January 1992. However, with the exception of one study of self-reported symptoms which showed only a small increase in risk,[1] large epidemiological studies,[2-5] meta-analyses,[6-8] and a review by the Medical Devices Agency in the UK have so far failed to show any association between silicone breast implants and connective tissue disorders. After conducting a review of the evidence, the FDA in 2006 re-approved the sale of silicone breast implants, for use in women of all ages for breast reconstruction, and for cosmetic use in women aged 22 years or more;[9] the approval obliges the manufacturers to conduct a 10-year post-approval safety study.

1. Hennekens CH, *et al.* Self-reported breast implants and connective-tissue diseases in female health professionals: a retrospective cohort study. *JAMA* 1996; 275: 616–21.
2. Gabriel SE, *et al.* Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 1994; 330: 1697–1702.
3. Sánchez-Guerrero J, *et al.* Silicone breast implants and the risk of connective-tissue diseases and symptoms. *N Engl J Med* 1995; 332: 1666–70.
4. Silverman BG, *et al.* Reported complications of silicone gel breast implants: an epidemiologic review. *Ann Intern Med* 1996; 124: 744–56.
5. Nyrén O, *et al.* Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. *BMJ* 1998; 316: 417–22.
6. Janowsky EC, *et al.* Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. *N Engl J Med* 2000; 342: 781–90.
7. Lipworth L, *et al.* Silicone breast implants and connective tissue disease: an updated review of the epidemiologic evidence. *Ann Plast Surg* 2004; 52: 598–601.
8. Lipworth L, *et al.* Breast implants and fibromyalgia: a review of the epidemiological evidence. *Ann Plast Surg* 2004; 52: 284–7.
9. FDA. FDA approves silicone gel-filled breast implants after in-depth evaluation (issued 17/11/06). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108790.htm (accessed 23/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aerogal; Darin-KA; EpiDerm; Europiel; Finescar; Kurapel; Skinderm SIL; Xeragel; *Austral.*: Cica-Care; *Dermatix*; Egozite Protective Baby Lotion†; Hospital Skin Care Lotion; Kelo-cote; Mepiform; NYDA; Rosken Skin Repair; Silic 15; *Belg.*: Mepitel; *Braz.*: Skimatix; *Canad.*: Barriere; Clinique Comfort†; Comfort Shield; Dermatix Si†; Dermatix Ultra; Proshield Plus; Readybath; Readycleanse; Sween 24; *Chile*: Epi-Derm; Lomprax; Neogasol; Para†; Sensei; *Fr.*: Cica-Care; Dermatix; Ophtasiloxane; *Ger.*: Dermatix; Jacutin; Mepiform; Mepilex; Mepitel; Nyda L; Siluron; Symadal M; *Hong Kong*: Dermatix; Egozite Protective Baby Lotion†; Silic 15; Skin Repair†; Uni-Methicone†; *Hung.*: Dermatix; *Indon.*: Dermatix; *Irl.*: Dermatix; *Israel*: Hedrin; *Ital.*: Cica-Care; Mepiform; Mepitel; *Malaysia*: Dermatix; Egozite Protective Baby Lotion†; Silic 15; *Mex.*: Dermatix Ultra; *Neth.*: SIL-1000, -5000; XT Luis; *NZ*: DP Barrier Cream†; Egozite Protective Baby Lotion; *Philipp.*: Cica-Care; Dermatix; *Pol.*: Silol†; *Port.*: Piky; *Singapore*: Dermatix; Rosken Skin Repair; Silic 15; Stratuderm; *UK*: Cica-Care; Dermatix; Hedrin; Linicin; Mepiform; NYDA; Pro-Sil; Silgel; *Ukr.*: Headring (Хедринг); *USA*: 4-N-1; Mentholatum Softlips; Pro-Q.

Multi-ingredient Preparations. *Arg.*: Assy Max; Basta; Hyalomatrix-PA; Kelo-Cote; Nopucid Bio Citrus; Nopucid Bio II; Sumo Full Contact; Talquisedan; *Austral.*: Dermalife Plus†; Dimethicream; Eczema Cream; Egozite Baby Cream; Hamilton Pine Tar with Menthol; *Austria*: Ceolat Compositum; *Braz.*: Balmex; Cicaplast; *Canad.*: Blistex Lip Balm; Blistex Ultra Protection Lip Balm; Gold Bond Anti-Itch; Gold Bond Extra Strength Medicated; Gold Bond Medicated; Moisturel; *Chile*: Aero Itan; Balsamo Analgesico con Fenilbutazona; Blisprotex; Exomega Barrera; Neopankreoflat; Talquisedan; Ureadin 30; Xeragel; *Denm.*: Silan; *Fr.*: Cicatridine; Flex-Tonic; Kelo-Cote; *Ger.*: Densiron 68; Dimet; EtoPril; Itax†; Kelo-Cote; *Gr.*: Rikospray Silicone; *Hong Kong*: 2nd Skin ScarGel; Dermatix Ultra; DS Emulsion†; Egozite Baby Cream; Hamilton Skin Repair†; Natamin C†; Vasogen†; *India*: Biolite; Calyx; Diafoot; Dibi; KC-Lite; Nestosule-MV; Siloderm; Tinidafyl Plus; *Indon.*: Kelo-Cote; Sodermix; *Irl.*: Cymex; Sprilon; Vasogen†; *Israel*: Kamil Blue; Kamil Blue; Kelo-Cote; *Ital.*: Angstrom Viso; Plurilac; Rikospray; *Malaysia*: Egozite Baby Cream; Norash; Palmer's Cocoa Butter Formula Scar Serum; QV Lip Balm; *Mon.*: Dermo Silanols; *NZ*: Egoderm; Egozite Baby; Rosken Skin Repair; Silic; *Philipp.*: Dermatix Ultra; *S.Afr.*: Arola Rosebalm†; Siopel; *Singapore*: Dermatix Ultra; Egozite Baby Cream; Metanium Everyday Barrier; Norash; Scar Esthetique; *Spain*: Dermo H Infantil†; Proskin; Silidermil; *Swed.*: Silon; *Switz.*: Kelo-cote†; *UK*: Conotrane; Cymex; Full Marks Solution; Lyclear Mousse; Lyclear Spray; Siopel; Sprilon; Vasogen; *USA*: A+D Zinc Oxide Cream; Blistex Lip Balm; ControlRx; Diaper Guard; Dyprotex; Gold Bond Intensive Healing; Gold Bond Medicated Triple Action Relief; Herpecin-L; Lansinoh Diaper Rash; Maxilube; Mentholatum Cherry Ice; Mentholatum Natural Ice; Mentholatum Softlips Lipbalm (UV); Mentholatum Softlips Lipbalm; Neosalus; Soothe & Cool; *Venez.*: Hidribet.

Sodium Cetostearyl Sulfate

Cetoestearilsulfato de sodio; Cétostéaryle (sulfate de) sodique; Cetylstearylschwefelsaures Natrium; Natrii Cetyloet Stearylosulfas; Natrio cetostearilo sulfatas; Natrium Cetylosulphuricum; Natrium Cetylstearylosulphuricum; Nátrium-cetil-sztearil-szulfát; Natriumcetostearylsulfat; Natriumcetylstearylsulfat; Natrium-cetylstearyl-sulfát; Natriumsetostearyylisulfaatti; Sodium Cetearyl Sulfate; Sodium Cetostearyl Sulphate; Sodu cetostearylosiarczan; Натрия Цетостеарилсульфат.

CAS — 59186-41-3 (sodium cetostearyl sulfate); 68955-20-4 (sodium mono-C16-18-alkyl sulfates); 1120-01-0 (sodium cetyl sulfate); 1120-04-3 (sodium stearyl sulfate).
UNII — 7Z8S068H48.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sodium Cetostearyl Sulfate). A mixture of sodium cetyl sulfate ($C_{16}H_{33}NaO_4S = 344.5$) and sodium stearyl sulfate ($C_{18}H_{37}NaO_4S = 372.5$). A white or pale yellow, amorphous or crystalline powder. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; partly soluble in alcohol.

USNF 31: (Sodium Cetostearyl Sulfate). A mixture of sodium cetyl sulfate ($C_{16}H_{33}NaSO_4 = 344.5$) and sodium stearyl sulfate ($C_{18}H_{37}NaSO_4 = 372.5$). It contains not less than 40% of sodium cetyl sulfate and the sum of the sodium cetyl sulfate content and sodium stearyl sulfate content is not less than 90%, both contents calculated on the anhydrous basis. A white or pale yellow, amorphous or crystalline powder. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; partly soluble in alcohol.

Profile

Sodium cetostearyl sulfate is an alkyl sulfate anionic surfactant (p. 2164.1). It is used as an oil-in-water emulsifier and as a detergent and wetting agent.

Sodium Cocoyl Isetionate

Sodium Cocoyl Isethionate; Кокоил Изетионат Натрия.
CAS — 61789-32-0.
UNII — 518XTE8493.

Sodium Lauroyl Isetionate

Sodium Lauroyl Isethionate; Sodium Lauroylisethionate; Sodium Lauryl Isethionate; Sodium 2-Sulfoethyl Laurate. Sodium 2-sulfoethyldodecanoate.
$C_{14}H_{27}NaO_5S = 330.4$
CAS — 7381-01-3.
UNII — M590021Z02.

Profile

Sodium cocoyl isetionate is the sodium salt of sulfoethyl esters of coconut oil fatty acids. It is an alkyl sulfonate anionic surfactant (p. 2164.1) and is used as a soap substitute. Sodium lauroyl isetionate, which is derived from lauric acid, and ammonium cocoyl isetionate have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hong Kong*: Physiogel; *Indon.*: Physiogel†; *Ital.*: Physiogel; *Philipp.*: Physiogel; *Thai.*: Physiogel†.

Multi-ingredient Preparations. *Mex.*: Bonaven.

Sodium Cocoyl Sarcosinate

CAS — 61791-59-1.
UNII — 1R9DUY89CZ.

Sodium Lauroyl Sarcosinate

Sodium Lauroylsarcosinate; Лаурилсаркозинат Натрия.
Sodium *N*-dodecanoyl-*N*-methylglycine.
$C_{15}H_{29}NNaO_3 = 294.4$
CAS — 137-16-6.
UNII — 632G599618.

Profile

Sodium cocoyl sarcosinate is an alkyl sarcosinate anionic surfactant (p. 2164.1) and is used as a soap substitute. Sodium lauroyl sarcosinate has been used similarly.

Sodium Laurilsulfate *(pINNM)*

Laurilsulfate de Sodium; Laurilsulfato de Sódio; Laurilsulfato de sodio; Natrii Laurilsulfas; Natrio laurilsulfatas; Natrium-Lauryl Sulphuricum; Natriumdodecylsulfat; Natriumlaurilsulfat; Nátrium-lauril-szulfát; Natrium-lauryl-sulfát; Natriumlauryylisulfaatti; Sodium Dodecyl Sulphate; Sodium laurilsulfate de; Sodium Lauryl Sulfate; Sodium Lauryl Sulphate; Sodu dodecylosiarczan; Sodu laurylosiarczan; Натрий Лаурилсульфат.

CAS — 151-21-3.
UNII — 368GB5141J.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Sodium Laurilsulfate; Sodium Lauryl Sulfate BP 2014). A mixture of sodium alkyl sulfates, consisting mainly of sodium dodecyl sulfate ($C_{12}H_{25}NaO_4S = 288.4$). It contains not less than 85% of sodium alkyl sulfates and not more than a total of 8% of sodium chloride and sodium sulfate. A white or pale yellow powder or crystals. Freely soluble in water giving an opalescent solution; partly soluble in alcohol.

USNF 31: (Sodium Lauryl Sulfate). A mixture of sodium alkyl sulfates, consisting mainly of sodium laurilsulfate ($C_{12}H_{25}NaO_4S = 288.4$). The combined content of sodium

chloride and sodium sulfate is not more than 8%. Small, white or light yellow crystals with a slight, characteristic odour. Soluble 1 in 10 of water giving an opalescent solution.

Incompatibility. Sodium laurilsulfate interacts with cationic surfactants such as cetrimide, resulting in a loss of activity. It is also incompatible with salts of polyvalent metal ions (e.g. aluminium, lead, tin, or zinc) and with acids of pH below 2.5. It is not affected by hard water because of the solubility of the corresponding calcium and magnesium salts.

Uses

Sodium laurilsulfate is an alkyl sulfate anionic surfactant (p. 2164.1). It is a detergent and wetting agent, effective in both acid and alkaline solution and in hard water. It is used in medicated shampoos, as a skin cleanser, and in toothpastes, and in the preparation of Emulsifying Wax (p. 2184.1). It is also used as a tablet lubricant.

Other salts of laurilsulfate have been used for their surfactant properties. These include monoethanolamine, diolamine, and trolamine laurilsulfates, and magnesium and ammonium laurilsulfates.

Alkyl ether sulfates such as sodium lauril ether sulfate (sodium laureth sulfate) and ammonium laurll ether sulfate (ammonium laureth sulfate), are ethoxylated derivatives and are used similarly. Sodium lauril sulfoacetate, which contains a sulfonate rather than a sulfate group, and sodium lauril ether sulfosuccinate (disodium laureth sulfosuccinate), an ethoxylated sulfonate, are also used.

Sodium laurilsulfate and related surfactants are also included in some combination preparations used rectally for the management of constipation.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies laurilsulfate used as a laxative 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 02/11/11)

Adverse Effects

Prolonged exposure to sodium laurilsulfate may irritate the skin or mucous membranes. Hypersensitivity reactions have been reported.

Skin thinning and increased transepidermal water loss were seen in a study in 6 healthy subjects after application of Aqueous Cream BP twice daily for 4 weeks.[1] The effect was attributed to the preparation's content of sodium laurilsulfate; it was suggested that use of the cream as an emollient in patients with eczema should be reconsidered.

1. Tsang M, Guy RH. Effect of Aqueous Cream BP on human stratum corneum in vivo. *Br J Dermatol* 2010; 163: 954–8.

Hypersensitivity. Hypersensitivity reactions have been reported[1,2] after use of toothpastes containing sodium laurilsulfate. There has also been a report[3] of hypersensitivity associated with ingestion of sodium laurilsulfate as an excipient in an oral preparation.

1. Lee A-Y, *et al.* Two cases of allergic contact cheilitis from sodium lauryl sulfate in toothpaste. *Contact Dermatitis* 2000; 42: 111.
2. Ersoy M, *et al.* The allergy of toothpaste: a case report. *Allergol Immunopathol (Madr)* 2008; 36: 368–70.
3. Sugiura K, *et al.* Delayed-type hypersensitivity reactions due to sodium lauryl sulphate in omeprazole. *J Eur Acad Dermatol Venereol* 2009; 23: 610–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Euroclear; Lactofilm; Limectant; *Chile*: Solucion Detergente; *Fr.*: Saforelle†; *Hong Kong*: Lowila Cake†; *Mex.*: Aquanil; *Spain*: Anticerumen.

Multi-ingredient Preparations. *Arg.*: Caien†; Micronema; Nigalax; Nindem; Plus & Plus; Xicanil Control NP; *Austral.*: Fleet Micro-Enema†; Micolette; Microlax; Pinetarsol; *Austria*: Microklist; *Belg.*: Microlax; Neo-Sabenyl; *Canad.*: Aseptone 2; Microlax; Plax†; *Cz.*: Dermofug†; *Denm.*: Microlax; *Fin.*: Microlax; *Fr.*: Bactident†; Microlax; Ysol 206†; *Ger.*: Dermowas; Microklist; *Gr.*: Dermacide; Sabenyl; *Hong Kong*: Microlax†; *Indon.*: Laxarec; Microlax; Sodermix; *Irl.*: Dentinox Cradle Cap; Micolette; Microlax; *Israel*: Microlet; *Ital.*: Eso Zim; Merankol Pastiglie; Novilax; *Malaysia*: Dentinox Cradle Cap; pH Care; *Mex.*: Microlax; *Neth.*: Casen Mikroklysma†; Microlax; *Norw.*: Microlax; *NZ*: Microlax; *Pol.*: Rektiolax; *Port.*: Microlax; *Rus.*: Microlax (Микролакс); *Singapore*: Dentinox Cradle Cap; Microlax; *Spain*: Cliseran; Microlax; *Swed.*: Microlax; *Switz.*: Microklist; Microlax; *Turk.*: SH-206; *UK*: Dentinox Cradle Cap; Micolette; Microlax; Relaxit; *USA*: Bodi Kleen; Cetaklenz; Geri-Lav Free; Klout; Maxilube; Summer's Eve Post-Menstrual; Trichotine; Trimo-San; *Venez.*: Novafix.

Pharmacopoeial Preparations
BP 2014: Emulsifying Wax.

Sodium Oleate

E470a (sodium, potassium, and calcium salts of fatty acids); Oleato de sodio; Олеиновокислый натрий; Sodium 9*Z*-octadecenoate.

$C_{18}H_{33}NaO_2$ = 305.5.

CAS — 143-19-1 (sodium oleate); 143-18-0 (potassium oleate); 142-17-6 (calcium oleate); 557-07-3 (zinc oleate).

UNII — 399SL044HN.

Profile

Sodium oleate is an alkali-metal soap anionic surfactant (p. 2164.1). It is used as an emulsifier and has also been used as an ingredient in preparations for the symptomatic relief of haemorrhoids and pruritus ani. It is one of the main components of soaps made from olive oil.

Other salts of oleic acid that have been used in skin preparations include zinc oleate and potassium oleate. Sodium, potassium, and calcium oleate are used as emulsifiers and anticaking agents in food, and the calcium salt has also been used in nutritional supplements. Monoethanolamine oleate is used as a sclerosant (see p. 2562.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Cose-Anal; *Canad.*: Artecho†; *Neth.*: Epianal; *Norw.*: Alcos-Anal; *Swed.*: Alcos-Anal.

Sodium Starch Glycolate

Carboximetilalmidón sódico; Carboxymethylamidon sodique; Carboxymethylamylum natricum; Glicolato sódico de almidón; Karboksymetyloskrobia sodowa; Karboximetilkeményítő-nátrium; Karboxymethylškrob sodná sůl; Natriumstärkeglykolat; Natriumtärkkelysglykolaatti; Sodium Carboxymethyl Starch; Sodium Starch Glycollate; Starch Sodium Glycolate; Натрия гликолят крахмала.

CAS — 9063-38-7.

UNII — 5856J3G2A2 (sodium starch glycolate type A potato).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Sodium Starch Glycolate (Type A); Carboxymethylamylum Natricum A). The sodium salt of a cross-linked partly *O*-carboxymethylated potato starch. It contains 2.8 to 4.2% of sodium, calculated with reference to the substance washed with alcohol (80%) and dried. A fine, white or almost white, very hygroscopic, free-flowing powder. It forms a translucent suspension in water; practically insoluble in dichloromethane. pH of a 3.33% dispersion in water is 5.5 to 7.5. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Sodium Starch Glycolate (Type B); Carboxymethylamylum Natricum B). The sodium salt of a cross-linked partly *O*-carboxymethylated potato starch. It contains 2.0 to 3.4% of sodium, calculated with reference to the substance washed with alcohol (80%) and dried. A fine, white or almost white, very hygroscopic, free-flowing powder. It forms a translucent suspension in water; practically insoluble in dichloromethane. pH of a 3.33% dispersion in water is 3.0 to 5.0. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Sodium Starch Glycolate (Type C); Carboxymethylamylum Natricum C). The sodium salt of a cross-linked by physical dehydration, partly *O*-carboxymethylated starch. It contains 2.8 to 5.0% of sodium, calculated with reference to the substance washed with alcohol (80%) and dried. A fine, white or almost white, very hygroscopic, free-flowing powder. It forms a translucent gel-like product in water; practically insoluble in dichloromethane. pH of a 3.33% gel in water is 5.5 to 7.5. Store in airtight containers. Protect from light.

USNF 31: (Sodium Starch Glycolate). The sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch. It may contain not more than 7.0% of sodium chloride. The sodium content is 2.8 to 4.2% (Type A) or 2.0 to 3.4% (Type B). pH of a 1 g in 30 mL suspension in water is between 5.5 and 7.5 (Type A) or between 3.0 and 5.0 (Type B).

A white, odourless, relatively free-flowing powder available in several different viscosity grades. A 2% dispersion in cold water settles, on standing, in the form of a highly hydrated layer. Protect from wide variations in temperature and humidity which may cause caking.

Profile

Sodium starch glycolate is used as a disintegrating agent in tablet manufacture.

Sodium Stearate

E470a (sodium, potassium, and calcium salts of fatty acids); Estearato de sodio; Natril-Stearat; Natrio stearatas; Natriumstearaatti; Natriumstearat; Sodium stearate; del Sodu stearynian; Stearan sodný; Stearato di Sodio; Стеарат натрия.

Sodium Octadecanoate.

CAS — 408-35-5 (sodium palmitate); 822-16-2 (sodium stearate).

UNII — QU7E2XA9TG.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Sodium Stearate). A mixture of sodium salts of different fatty acids consisting mainly of stearic acid ($C_{18}H_{35}O_2Na = 306.5$) and palmitic acid ($C_{16}H_{31}O_2Na = 278.4$). It contains 7.4 to 8.5% of sodium, calculated with reference to the dried substance. The fatty acid fraction contains not less than 40% of stearic acid and the sum of stearic acid and palmitic acid is not less than 90%. A white or yellowish, fine powder, with a greasy touch. Slightly soluble in water and in alcohol. Store in airtight containers. Protect from light.

USNF 31: (Sodium Stearate). A mixture containing not less than 90% of sodium stearate ($C_{18}H_{35}NaO_2 = 306.5$) and sodium palmitate ($C_{16}H_{31}NaO_2 = 278.4$); the content of sodium stearate is not less than 40% of the total. It contains small amounts of the sodium salts of other fatty acids. A fine, white powder, soapy to the touch, usually with a slight tallow-like odour. Slowly soluble in cold water and in cold alcohol; readily soluble in hot water and in hot alcohol. Protect from light.

Profile

Sodium stearate is an alkali-metal soap anionic surfactant (p. 2164.1) used as an emulsifying and stiffening agent in a variety of topical and rectal preparations. It is also used as an emulsifier in foods and is one of the main components of soaps produced from animal fats. Potassium stearate has been used similarly.

Preparations

Pharmacopoeial Preparations
USP 36: Glycerin Suppositories.

Sodium Stearyl Fumarate

Fumarato de estearilo y sodio; Natril Stearyls Fumaras; Natrio stearilfumaratas; Natriumstearylfumarat; Natrium-stearylfumarát; Natriumstearyylifumaraatti; Natrium-sztearil-fumarát; Stéaryle (fumarate de) sodique; Натрия стеарилфумарат.

Sodium monooctadecyl 2-butenedioate.

$C_{22}H_{39}NaO_4$ = 390.5.

CAS — 4070-80-8.

UNII — 7CV7WJK4UI.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Sodium Stearyl Fumarate). A fine, white or almost white powder with agglomerates of flat, circular shaped particles. Practically insoluble in water, in alcohol, and in acetone; slightly soluble in methyl alcohol.

USNF 31: (Sodium Stearyl Fumarate). A fine white powder. Practically insoluble in water; slightly soluble in methyl alcohol.

Profile

Sodium stearyl fumarate, the sodium salt of the stearate ester of fumaric acid, is an ester carboxylate anionic surfactant (p. 2164.1). It is used as a lubricant in the manufacture of tablets and capsules, and is also used in foods and cosmetics.

Soft Paraffin

INS No. 905b (petroleum jelly).

NOTE. The code 905 has been used for mineral hydrocarbons including soft paraffin but E905 is now used specifically for microcrystalline wax (p. 2198.1).

White Soft Paraffin

905; (mineral hydrocarbons); Minkštasis baltas parafinas; Paraff. Moll. Alb.; Parafinum Molle Album; Parafina blanda blanca; Valkovaseliini; Vaselin, vitt; Vaselina blanca; Vaselina Branca; Vaselina filante; Vaseline blanche; Vaseline Officinale; Vaselinum album; Vazelína bílá; Wazelina biała; White Petrolatum; White Petroleum Jelly; Белый вазелин.

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

Many pharmacopoeias use the title Vaselinum Album; in some countries the name 'Vaseline' is a trade-mark.

Ph. Eur. 8: (Paraffin, White Soft). Purified and wholly or nearly decolorised mixture of semi-solid hydrocarbons, obtained from petroleum. It may contain a suitable antoxidant. It is not suitable for oral use. A white or almost white, translucent, soft unctuous mass, slightly fluorescent in daylight when melted. Drop point 35 degrees to 70 degrees. Practically insoluble in water, in alcohol, and in glycerol; slightly soluble in dichloromethane. Protect from light.

The BP 2014 gives White Petroleum Jelly as an approved synonym.

USP 36: (White Petrolatum). A purified mixture of semisolid hydrocarbons obtained from petroleum, and wholly or nearly decolorised. It may contain a suitable stabiliser. A white or faintly yellowish unctuous mass, transparent in thin layers even after cooling to 0 degrees. Insoluble in water; slightly soluble in cold or hot alcohol and in cold dehydrated alcohol; freely soluble in chloroform, in benzene, and in carbon disulfide; soluble in ether, in petroleum spirit, and in most fixed and volatile oils.

Yellow Soft Paraffin

Keltavaseliini; Minkštasis geltonas parafinas; Paraff. Moll. Flav.; Paraffinum Molle Flavum; Petrolatum; Petroleum Jelly; Sárga vazelin; Vaselin, gult; Vaselina Amarela; Vaselina amarilla; Vaselina filante amarilla; Vaseline jaune; Vaselinum Flavum; Vazelína žlutá; Wazelina żółta; Yellow Petrolatum; Yellow Petroleum Jelly; Жёлтый Вазелин.

CAS — 8009-03-8.

UNII — 4T6H12BN9U.

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

Many pharmacopoeias use the title Vaselinum Flavum; in some countries the name 'Vaseline' is a trade-mark.

Ph. Eur. 8: (Paraffin, Yellow Soft). A purified mixture of semi-solid hydrocarbons obtained from petroleum. A yellow, translucent, unctuous mass, slightly fluorescent in daylight when melted. It has a drop point of 40 degrees to 60 degrees. Practically insoluble in water, in alcohol, and in glycerol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Petrolatum). A purified mixture of semi-solid hydrocarbons obtained from petroleum. It may contain a suitable stabiliser. It is an unctuous yellowish to light amber mass, having not more than a slight fluorescence even after being melted. It is transparent in thin layers. It is free or practically free from odour. M.p. 38 degrees to 60 degrees. Insoluble in water; practically insoluble in cold or hot alcohol and in cold dehydrated alcohol; freely soluble in benzene, in carbon disulfide, in chloroform, and in turpentine oil; soluble in ether, in petroleum spirit, and in most fixed and volatile oils.

Uses and Administration

Soft paraffin is used as an ointment basis and as an emollient in the management of skin disorders. It is not readily absorbed by the skin. Sterile dressings containing soft paraffin are used for wound dressing and as a packing material. Soft paraffin is also included in ointments used as ophthalmic lubricants in the management of dry eye (p. 2190.1). Application of soft paraffin has been used for the eradication of pubic lice from the eyelashes (see Pediculosis, p. 2147.3). It has been used as a contact medium to reduce pain during extracorporeal shock wave lithotripsy. Soft paraffin is also used in food manufacturing.

Adverse Effects

Adverse effects of soft paraffin are rare when used in topical preparations, but sensitivity reactions and acne have been reported after topical use. Granulomatous reactions after absorption or injection and lipoid pneumonia after aspiration have occurred.

Fire risk. Burns to the scalp, face, and hands have been reported[1] in 5 patients who accidentally ignited their hair after the application of paraffin-based hair grease. Four patients suffered inhalation injury, 2 of whom required intubation. The death of a patient who, while smoking, ignited bandages covering a paraffin-based ointment for psoriasis,[2] prompted the *BNF* to recommend that patients should be told not to smoke and to keep away from flames when using paraffin-based emollients.

1. Bascom R, *et al.* Inhalation injury related to use of petrolatum-based hair grease. *J Burn Care Rehabil* 1984; 5: 327–30.
2. National Patient Safety Agency. Managing the fire hazard with paraffin based skin products on dressings and clothing (issued on 26 November 2007). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60266&type=full&servicetype=Attachment (accessed 23/08/10)

Hypersensitivity. The allergenicity of soft paraffin products has been investigated.[1–4] Considering their widespread use there are very few reports of sensitivity;[4] of nearly 80 000 patients patch tested with white soft paraffin, only 29 showed a positive reaction. White soft paraffin is generally less sensitising than yellow soft paraffin, although allergenicity differs from product to product. The allergenic components are probably polycyclic aromatic hydrocarbons present as impurities and quantities found in a particular paraffin depend on the source and purification method. Only the purest forms should be used in pharmaceuticals, cosmetics, and for patch testing, and highly purified white soft paraffin is preferred to yellow soft paraffin.

1. Dooms-Goossens A, Degreef H. Contact allergy to petrolatums (I). Sensitising capacity of different brands of yellow and white petrolatums. *Contact Dermatitis* 1983; 9: 175–85.
2. Dooms-Goossens A, Degreef H. Contact allergy to petrolatums (II). Attempts to identify the nature of the allergens. *Contact Dermatitis* 1983; 9: 247–56.
3. Dooms-Goossens A, Dooms M. Contact allergy to petrolatums (III). Allergenicity prediction and pharmacopoeial requirements. *Contact Dermatitis* 1983; 9: 352–9.
4. Schnuch A, *et al.* White petrolatum (Ph. Eur.) is virtually non-sensitizing: analysis of IVDK data on 80 000 patients tested between 1992 and 2004 and short discussion of identification and designation of allergens. *Contact Dermatitis* 2006; 54: 338–43.

Lipoid pneumonia. Various uses of soft paraffin have been associated with lipoid pneumonia, including topical facial use to treat psoriasis,[1] long-term intranasal application for a dry nose,[2] and use as a lubricant during nasogastric intubation.[3]

1. Cohen MA, *et al.* Exogenous lipoid pneumonia caused by facial application of petrolatum. *J Am Acad Dermatol* 2003; 49: 1128–30.
2. Brown AC, *et al.* Exogenous lipoid pneumonia due to nasal application of petroleum jelly. *Chest* 1994; 105: 968–9.
3. Bernabeu Mora R, *et al.* Neumonía lipoidea aguda debiba a la aspiratión accidental de vaselina utilizada en un sondaje nasogástrico. *Arch Bronconeumol* 2000; 36: 485–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Jelonet; ***Braz.***: Vaselina; ***Canad.***: Cetraben†; Critic-Aid Clear; Prevex; Protective Ointment; Summerberry Skin Cream; Vaseline; ***Fr.***: Jelonet; Tulle Gras; Vaselitulle; ***Ger.***: Oleo Tull; ***Gr.***: Vaseline Pure; ***Irl.***: Dermamist; ***Ital.***: Adaptic; Jelonet; Lomatuell H; ***Mex.***: Formula Dermica; Lubrilin†; ***Philipp.***: Apollo; ***Rus.***: Kliotex (Клиотекс); ***S.Afr.***: Jelonet; ***Spain***: Lacrilube; Vasfilm; ***Turk.***: Duratears; ***UK***: Dermamist; Jelonet; Vaseline; ***USA***: Ocu-Lube.

Multi-ingredient Preparations. ***Arg.***: Alcon Lagrimas; Aqualane; Benzalcrem; Macoderm; Milorix†; ***Austral.***: Dermeze; E45; Epaderm; Epaderm; Granugen†; Ircal; Lacri-Lube; Poly Visc; QV Flare Up; Triple Care Cream; ***Austria***: Tiroler Steinol; ***Belg.***: Duratears; Lacrytube; Transitol; ***Canad.***: A & D Ointment; Akwa Tears; Bum-Butt-R; Duolube; Everything Butt; Flexitol Heel Balm†; Hydrophil; Hypotears; Moisturel; Optilube; Refresh Lacri-Lube; Sebamed; Tears Naturale PM; ***Chile***: Chapstick Medicated; Durasolets; Duratears; Ictyane; Lacri-Lube; Pasta Lassar; ***Denm.***: Ojensalve Neutral; ***Fin.***: Lacri-Lube; ***Fr.***: Cellosorb†; Codexial Zinc†; Dexeryl; Grassolind Neutral; Ictyane HD; Ictyane; Transitol; Transulose; Vaseline Gomenolee; ***Ger.***: Coliquifilm; Dexeryl; Sofra-Tull sine; Vita-POS; ***Gr.***: Duratears; Vaseline Borique; Vaseline Oxyde Zinc; ***Hong Kong***: Duratears; Oilatum Cream; ***India***: Adlube; Cetraben; Dermoys; Dershine; Dewee; ***Elsoft***; Emoderm; ***Himost***; ***Leoben***: Microgard Tulle; Moitz; Moyzen; Oilatum; ***Irl.***: Lacri-Lube; Oilatum Cream; Silcocks Base; ***Israel***: Duratears; Kamil Blue; Lacrimol†; Vita-POS; ***Ital.***: Lacrilube; Transitol; Transulose; ***Malaysia***: Aqua Cream; Balneum†; Duratears Naturale; Lacrilube; Oilatum; Palmer's Cocoa Butter Formula Nappy Rash Ointment; Palmer's Cocoa Butter Formula Nursing Cream; QV Lip Balm; ***Mex.***: Transilax; ***Neth.***: Duratears Z; Transulose; ***Norw.***: Simplex; ***NZ***: Lacrilube; Poly-Visc; ***Philipp.***: Oilatum; ***Pol.***: Amfobase†; Diprobase; E45; Unibasis; ***Singapore***: Balneum; Duratears; Lacrilube†; Metanium Everyday Barrier; Oilatum Cream; ***Spain***: Lubrifilm†; Vaselina Boricada†; ***Switz.***: Coliquifilm; Dexeryl; ***Thai.***: Duratears; Oilatum Cream†; ***Turk.***: Cinkos; ***UK***: 50:50; Cetraben Emollient; Diprobase; Emollin; Epaderm; Hewletts†; Hydromol; Imuderm†; Lacri-Lube; Lubri-Tears†; Melrose; Oilatum Cream; Oilatum Junior; VitA-POS; Zerocream; Zeroguent; ***Ukr.***: Transuloza (Трансулоза); ***USA***: Akwa Tears†; Albolene; Aquaphor Healing Ointment; Aquaphor†; ARC; Bodi Care Lotion; Bottom Better†; Boudreaux's Butt Paste; Chapstick Medicated Lip Balm; DermaPhor; Desitin Creamy; Diaper Guard; Dry Eyes; Duratears Naturale; Formulation R; Hemorid For Women; Hemorid For Women; Hydrocerin; Hypotears; Lacri-Gel; Lacri-Lube; LubriFresh PM; LubriTears; Paladin; Palomar E; Puralube; Refresh Lacri-Lube; Refresh PM; Soothe Night Time; Stye; Systane Nighttime; Tears Again; Tears Renewed†; Venelex.

Pharmacopoeial Preparations

BP 2014: Cetomacrogol Emulsifying Ointment; Cetrimide Emulsifying Ointment; Emulsifying Ointment; Paraffin Ointment; Simple Eye Ointment; Simple Ointment; Wool Alcohols Ointment;

USP 36: Bland Lubricating Ophthalmic Ointment; Hydrophilic Ointment; Hydrophilic Petrolatum; Petrolatum Gauze; White Ointment; Yellow Ointment.

Soft Soap

Green Soap; Jabón blando; Jabón verde; Medicinal Soft Soap; Sabão Mole; Sapo Mollis; Калиевое Мыло; Зелёное Мыло.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2014: (Soft Soap). It is made by the interaction of potassium hydroxide or sodium hydroxide with a suitable vegetable oil or oils or their fatty acids. It may be coloured with chlorophyll or not more than 0.015% of a suitable green soap dye. A yellowish-white to green or brown, unctuous substance. Soluble in water and in alcohol.

USP 36: (Green Soap). It is made by the saponification of suitable vegetable oils, excluding coconut oil and palm kernel oil, without the removal of glycerol. The method given in the USP 36 involves mixing the oil with oleic acid and to the heated mixture adding potassium hydroxide dissolved in glycerol and water. The homogeneous emulsion is then adjusted to weight with hot water. A yellowish-white to brownish- or greenish-yellow, transparent to translucent, soft unctuous mass with a slight, characteristic odour.

Uses

The name soap may be applied to a range of anionic surfactants (p. 2164.1) used for their detergent properties. The characteristics of soaps differ depending on the fatty acids they are derived from, the alkali used in their preparation, and whether they contain glycerol (a byproduct of their manufacture). Soaps defined in pharmacopoeias vary in the fatty acids allowed and whether they are sodium salts, potassium salts (potassium soap), or either.

Soft soaps contain glycerol and have been used to remove incrustations in chronic scaly skin diseases such as psoriasis (p. 1688.1) and to cleanse the scalp before the application of lotions. A solution of soft soap in warm water has been used as an enema to soften impacted faeces but should be avoided as it may inflame the colonic mucosa; other measures are now preferred (see Constipation, p. 1804.3). Alcoholic solutions of soft soap, such as Soap Spirit (BP 2014) and Green Soap Tincture (USP 36), are used as skin cleansers and detergents. A similar product was formerly used as a liniment (Soap Liniment; Opodeldoc).

Other soaps with pharmaceutical applications include: potash soap (linseed oil soap) made from linseed oil and potassium hydroxide, which has been used in the preparation of liquid soaps; hard soap (castile soap), made from olive oil and sodium hydroxide with glycerol removed, which has been used as a tablet excipient and in the preparation of plasters; and curd soap, made from animal fat and sodium hydroxide with glycerol removed, which has been used as a tablet excipient.

Adverse Effects and Treatment

Soaps, and anionic detergents in general, may be irritant to the skin by removing natural oils and may produce redness, soreness, cracking and scaling, and papular dermatitis. There may be some irritation of the mucous membranes and because of this soap enemas are no longer recommended; marked irritation may occur if soaps or detergents enter the eye. Ingestion of anionic detergents may cause gastrointestinal irritation with nausea, diarrhoea, intestinal distension, and occasionally vomiting. Treatment is symptomatic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Waldheim Abfuhrdragees forte†; ***Spain***: Linimento Naion; ***USA***: Therevac Plus; Therevac SB.

Pharmacopoeial Preparations

BP 2014: Soap Spirit;

USP 36: Green Soap Tincture; Green Soap.

Solvent Ether

Aether; Aether Aethylicus; Aether Solvens; Diethyl Ether; Eetteri; Eter; Éter; Éter dietílico; Éter disolvente; Éter etílico; Éter ordinario; Eteris; Ether; Éther; Éther rectifié; Ethyl Ether; Ethyl Oxide; Etoxietano; Óxido dietílico; Этиловый Эфир; Диэтиловый Эфир.

$(C_2H_5)_2O$=74.12

CAS — 60-29-7.

UNII — 0F5N573A2Y.

NOTE. Solvent ether is not intended for anaesthesia; only ether of a suitable quality (see p. 1900.3) should be so used.

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

Ph. Eur. 8: (Ether). A colourless, clear, volatile, highly flammable liquid. It may contain a suitable non-volatile antoxidant at a suitable concentration. Relative density 0.714 to 0.716. Distillation range 34 degrees to 35 degrees. Soluble in water; miscible with alcohol, with dichloromethane, and with fatty oils. Store at 8 degrees to 15 degrees in airtight containers. Protect from light.

USP 36: (Ether). A colourless, mobile, volatile, flammable liquid, having a characteristic sweet, pungent odour. It is slowly oxidised by the action of air and light, with the formation of peroxides. B.p. about 35 degrees. Sp. gr. 0.713 to 0.716. Soluble 1 in 12 of water; miscible with alcohol, with chloroform, with dichloromethane, with petroleum spirit, with benzene, and with fixed and volatile oils; soluble in hydrochloric acid. Store in partly filled airtight containers at a temperature not exceeding 30 degrees and remote from fire. Protect from light.

Stability. Though ether is one of the lightest of liquids, its vapour is very heavy, being 2½ times heavier than air.

Ether is very volatile and flammable and mixtures of its vapour with oxygen, nitrous oxide, or air at certain concentrations are explosive. It should not be used in the presence of an open flame or any electrical apparatus liable to produce a spark; precautions should be taken against the production of static electrical discharge. Explosive peroxides are generated by the atmospheric oxidation of solvent ether and it is dangerous to distil a sample that contains peroxides.

Uses

Solvent ether is widely used as a pharmaceutical and industrial solvent, and is used as an extraction solvent in food processing.

Adverse Effects

As for Anaesthetic Ether, p. 1901.1. Ingestion of 30 to 60 mL may be fatal.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Prosceptine†.

Multi-ingredient Preparations. *Ger.*: Hoffmannstropfen; *S.Afr.*: Chamberlains Traditional Colic Remedy††; Krampdruppels; Moultons Pain Paint†.

Sorbitan Esters

Sorbitan, ésteres de; Эфиры Сорбитана.

Description. A series of mixtures of the partial esters of sorbitol and its mono- and di-anhydrides with fatty acids.

Sorbitan Laurate *(BAN, rINN)*

E493; Laurato de sorbitán; Monolaurato de sorbitán; Sorbitaanilauraatti; Sorbitan, laurate de; Sorbitan, laurato de; Sorbitan Monododecanoate; Sorbitan Monolaurate (USAN); Sorbitani Lauras; Sorbitanlaurat; Sorbitan-laurát; Sorbitanmonolaurat; Sorbitano lauratas; Szorbitán-laurát; Сорбитана Лаурат.

$C_{18}H_{34}O_6$ (approximate)

CAS — 1338-39-2.

UNII — 6W9PS8B71J.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Laurate). A mixture of the partial esters of sorbitol and its mono- and di-anhydrides with lauric acid. A brownish-yellow viscous liquid. Relative density about 0.98. Practically insoluble but dispersible in water; miscible with alcohol; slightly soluble in cottonseed oil. Protect from light.

USNF 31: (Sorbitan Monolaurate). A partial ester of sorbitol and its mono-and di-anhydrides with lauric acid. A yellow to amber oily liquid with a bland characteristic odour. Insoluble in water; soluble in liquid paraffin; slightly soluble in cottonseed oil and in ethyl acetate. Store in airtight containers.

Sorbitan Oleate *(BAN, rINN)*

E494; Monooleato de sorbitán; NSC-406239; Oleato de sorbitán; Sorbitaanioleaatti; Sorbitan Mono-9-octadecenoate; Sorbitan Mono-oleate; Sorbitan Monooleate (USAN); Sorbitan, oléate de; Sorbitán, oleato de; Sorbitani oleas; Sorbitanmonooleat; Sorbitano oleatas; Sorbitanoleat; Sorbitan-oleát; Szorbitán-oleát; Сорбитана Олеат.

$C_{24}H_{44}O_6$ (approximate)

CAS — 1338-43-8.

UNII — 06XEA2VD5G.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Oleate). A mixture usually obtained by esterification of 1 mole of sorbitol and its mono- and di-anhydrides per mole of oleic acid. A suitable antoxidant may be added. A brownish-yellow viscous liquid. Relative density about 0.99. Practically insoluble but dispersible in water; miscible with alcohol; soluble in fatty oils producing a hazy solution. Protect from light.

USNF 31: (Sorbitan Monooleate). A partial oleate ester of sorbitol and its mono- and di-anhydrides. A yellow to amber-coloured, viscous, oily liquid with a bland characteristic odour. Insoluble in water and in propylene glycol; miscible with mineral and vegetable oils. Store in airtight containers.

Sorbitan Palmitate *(BAN, rINN)*

E495; Monopalmitato de sorbitan; Palmitato de sorbitán; Sorbitaanipalmitaatti; Sorbitan Monohexadecanoate; Sorbitan Monopalmitate (USAN); Sorbitan, Palmitate de; Sorbitán, palmitato de; Sorbitani Palmitas; Sorbitanmonopalmitat; Sorbitano palmitatas; Sorbitanpalmitat; Sorbitan-palmitát; Szorbitán-palmitát; Сорбитана Пальмитат.

$C_{22}H_{42}O_6$ (approximate)

CAS — 26266-57-9.

UNII — 7766Z42JKU.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Palmitate). A mixture of the partial esters of sorbitol and its mono- and di-anhydrides with palmitic acid. A yellowish or yellow powder, waxy flakes, or hard masses. M.p. 44 degrees to 51 degrees. Practically insoluble in water; slightly soluble in alcohol; soluble in fatty oils. Protect from light.

USNF 31: (Sorbitan Monopalmitate). A partial ester of sorbitol and its mono- and di-anhydrides with palmitic acid. A cream-coloured, waxy solid with a faint fatty odour. Insoluble in water; soluble in warm dehydrated alcohol; soluble with haze in warm liquid paraffin and in warm arachis oil.

Sorbitan Sesquioleate *(BAN, USAN, rINN)*

A mixture of sorbitan mono-9-octadecenoate and sorbitan di-9-octadecenoate; Sesquioleato de sorbitán; Sorbitaaniseskvioleaatti; Sorbitan, sesquioléate de; Sorbitán, sesquioleato de; Sorbitani Sesquioleas; Sorbitano seskvioleatas; Sorbitanseskvioleat; Sorbitan-seskvioleát; Sorbitanseskvioleat; Szorbitán-szeszkvioleát; Сорбитана Сесквиолеат.

$C_{33}H_{60}O_6$ (approximate)

CAS — 8007-43-0.

UNII — 0W8RRISW5A.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Sorbitan Sesquioleate). A mixture usually obtained by esterification of 2 moles of sorbitol and its mono-and di-anhydrides per 3 moles of oleic acid. A suitable antoxidant may be added. Relative density about 0.99. A pale yellow or slightly brownish-yellow paste, which becomes a viscous, oily, brownish-yellow liquid at about 25 degrees. Dispersible in water; slightly soluble in dehydrated alcohol; soluble in fatty oils. Protect from light.

USNF 31: (Sorbitan Sesquioleate). A partial oleate ester of sorbitol and its mono- and di-anhydrides. A yellow to amber-coloured, oily viscous liquid. Insoluble in water and in propylene glycol; soluble in alcohol, in isopropyl alcohol, in cottonseed oil, and in liquid paraffin. Store in airtight containers.

Sorbitan Stearate *(BAN, rINN)*

E491; Estearato de sorbitán; Monoestearato de sorbitán; Sorbitaanistearaatti; Sorbitán, estearato de; Sorbitan Mono-octadecanoate; Sorbitan Monostearate (USAN); Sorbitan, stéarate de; Sorbitani Stearas; Sorbitanmonostearat; Sorbitano stearatas; Sorbitanstearát; Sorbitan-stearát; Szorbitán-sztearát; Сорбитана Стеарат.

$C_{24}H_{46}O_6$ (approximate)

CAS — 1338-41-6.

UNII — NVZ4I0H58X.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Stearate). A mixture of the partial esters of sorbitol and its mono- and di-anhydrides with stearic acid. A pale yellow, waxy solid. M.p. 50 degrees to 55 degrees. Practically insoluble but dispersible in water; slightly soluble in alcohol. Protect from light.

USNF 31: (Sorbitan Monostearate). A partial ester of sorbitol and its mono- and di-anhydrides with stearic acid. A cream-coloured to tan, hard, waxy solid with a bland odour. Insoluble in cold water and in acetone; dispersible in warm water; soluble, with haze, above 50 degrees in ethyl acetate and in liquid paraffin.

Sorbitan Trioleate *(BAN, USAN, rINN)*

Sorbitaanitrioleaatti; Sorbitan Tri-9-octadecenoate; Sorbitan, trioléate de; Sorbitán, trioleato de; Sorbitani Trioleas; Sorbitano trioleatas; Sorbitantrioleat; Sorbitan-trioleát; Szorbitán-trioleát; Trioleato de sorbitán; Сорбитана Триолеат.

$C_{60}H_{108}O_8$ (approximate)

CAS — 26266-58-0.

UNII — QE6F49RPJT.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Trioleate). A mixture usually obtained by esterification of 1 mole of sorbitol and its mono- and di-anhydrides per 3 moles of oleic acid. A suitable antoxidant may be added. A pale yellow, light yellowish or brown solid which becomes a brownish-yellow, viscous, oily liquid at about 25 degrees. Relative density about 0.98. Practically insoluble but dispersible in water; slightly soluble in alcohol; soluble in fatty oils. Protect from light.

USNF 31: (Sorbitan Trioleate). A tri-ester of sorbitol and its mono- and di-anhydrides with oleic acid. A yellow to amber-coloured, oily liquid. Insoluble in water, in ethylene glycol, and in propylene glycol; soluble in alcohol, in isopropyl alcohol, in methyl alcohol, in maize oil, in cottonseed oil, and in liquid paraffin. Store in airtight containers.

Sorbitan Tristearate *(BAN, USAN, rINN)*

E492; Sorbitán, triestearato de; Sorbitan Tri-octadecanoate; Sorbitan, Tristéarate de; Sorbitani Tristearas; Triestearato de sorbitán; Сорбитана Тристеарат.

$C_{60}H_{114}O_8$ (approximate)

CAS — 26658-19-5.

UNII — 6LUM696811.

Description. A mixture of the partial tri-esters of sorbitol and its mono- and di-anhydrides with stearic acid.

Uses

Sorbitan esters are polyalcohol ester nonionic surfactants (p. 2164.2). They are lipophilic and are used as emulsifying agents in the preparation of emulsions, creams, and ointments for pharmaceutical and cosmetic use. When used alone they produce stable water-in-oil emulsions but they are frequently used with a polysorbate in varying proportions to produce water-in-oil or oil-in-water emulsions or creams with a variety of different textures and consistencies. Sorbitan esters are also used as emulsifiers and stabilisers in food.

Adverse Effects

There have been occasional reports of hypersensitive skin reactions after the topical application of creams containing sorbitan esters.

Hypersensitivity. References.

1. Finn OA, Forsyth A. Contact dermatitis due to sorbitan monolaurate. *Contact Dermatitis* 1975; 1: 318.
2. Hannuksela M, *et al.* Allergy to ingredients of vehicles. *Contact Dermatitis* 1976; 2: 105–10.
3. Austad J. Allergic contact dermatitis to sorbitan monooleate (Span 80). *Contact Dermatitis* 1982; 8: 426–7.
4. Boyle J, Kennedy CTC. Contact urticaria and dermatitis to Alphaderm. *Contact Dermatitis* 1984; 10: 178.
5. Hardy MP, Maibach HI. Contact urticaria syndrome from sorbitan sesquioleate in a corticosteroid ointment. *Contact Dermatitis* 1995; 32: 114.
6. Wakelin SH, *et al.* Sorbitan mono-oleate: a potential allergen in paste bandages. *Contact Dermatitis* 1996; 35: 377.
7. de Waard-van der Spek FB, *et al.* Allergic contact dermatitis to sorbitan sesquioleate in Adapdc wound dressing. *Contact Dermatitis* 2007; 57: 54–6.
8. Asarch A, Scheinman PL. Sorbitan sesquioleate, a common emulsifier in topical corticosteroids, is an important contact allergen. *Dermatitis* 2008; 19: 323–7.
9. Asarch A, Scheinman PL. Sorbitan sesquioleate: an emerging contact allergen. *Dermatitis* 2008; 19: 339–41.
10. Castanedo-Tardan MP, Jacob SE. Allergic contact dermatitis to sorbitan sesquioleate in children. *Contact Dermatitis* 2008; 58: 171–2.

Squalane

Cosbiol; Dodecahydrosqualene; Escualano; Perhidroescualeno; Perhydrosqualène; Skvalaani; Skvalan; Skvalanas; Skwalan; Spinacane; Squalan; Squalanum; Szkvalán; Сквалан.

2,6,10,15,19,23-Hexamethyltetracosane.

$C_{30}H_{62}$=422.8

CAS — 111-01-3 (squalane); 111-02-4 (squalene).

UNII — GW89575KF9.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Squalane). A clear, colourless, oily liquid. Relative density about 0.815. It may be of vegetable (unsaponifiable matter of olive oil) or animal (shark liver oil) origin. Practically insoluble in water and in alcohol;

The symbol † denotes a preparation no longer actively marketed

freely soluble in acetone and in cyclohexane; miscible with most fats and oils.

USNF 31: (Squalane). A saturated hydrocarbon obtained by hydrogenation of squalene, an aliphatic triterpene occurring in some fish oils. It is a colourless, almost odourless, transparent oil. Insoluble in water; very slightly soluble in dehydrated alcohol; miscible with chloroform and with ether; slightly soluble in acetone. Store in airtight containers.

Profile

Squalane is a saturated derivative of squalene, a constituent of human sebum. It is miscible with human sebum and is included in topical preparations to increase skin permeability. It is also used as an emollient. Squalene is used similarly and has also been included in nutritional supplements for its supposed antoxidant effect. It is also used as an adjuvant in vaccines.

Adverse effects of squalene. There has been concern[1] about the potential adverse effects of squalene used as an adjuvant in vaccines, which some have attempted to link to the development of Gulf War syndrome after the detection of anti-squalene antibodies in vaccinees with this condition. However, it has been pointed out that in fact these patients had not been given squalene-containing vaccines, that squalene is a normal product of hepatic metabolism, and that antibodies to squalene develop in most adults regardless of whether they receive such vaccines.

1. WHO Global Advisory Committee on Vaccine Safety. Squalene-based adjuvants in vaccines (reviewed 03/12/08). Available at: http://www.who.int/vaccine_safety/topics/adjuvants/squalene/questions_and_answers/en/ (accessed 12/04/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Effaclar H; *Fr.*: Trioptec; *Hong Kong*: Physiogel; Tocovid; *India*: Arjet; Elure; Hidrate; Humidus; *Israel*: CleanEars; *Ital.*: Babygella; *Malaysia*: O'Yes; Tocovid Suprabio with DHA; Tocovid Suprabio; *Philipp.*: CleanEars; Tocovid Suprabio; *Port.*: Creme Laser Hidrante†; *Singapore*: Tocovid; *USA*: Mimyx†.

Stearic Acid

Acide stéarique; Acido Esteárico; Acido stearico; Acidum stearicum; Esteárico, ácido; Kwas stearowy; Kwas stearynowy; Kyselina stearová; Octadecanoic Acid; Steariinihappo; Stearik asit; Stearinezuur; Stearino rūgštis; Stearinsäure; Stearinsyra; Stearínskäbe; Sztearinsav; Стеаринова кислина; Стеариновая Кислота.

CAS — 57-11-4 (stearic acid); 57-10-3 (palmitic acid).
UNII — 4ELV7Z65AP.

NOTE. Stearic acid is sometimes incorrectly called 'stearine' in commerce.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

USNF also includes a purified form.

Ph. Eur. 8: (Stearic Acid). It is obtained from fat or oils from a vegetable or animal source and is a mixture consisting mainly of stearic acid ($C_{18}H_{36}O_2$ = 284.5) and palmitic acid. Stearic Acid 50 contains 40 to 60% stearic acid, the sum of the contents of stearic and palmitic acids being a minimum 90%. Stearic Acid 70 contains 60 to 80% stearic acid, the sum of the contents of stearic and palmitic acids being a minimum 90%. Stearic Acid 95 contains a minimum of 90% stearic acid, the sum of the contents of stearic and palmitic acids being a minimum 96%. White or almost white, waxy, flaky crystals, white or almost white, hard masses, or a white or yellowish-white powder. Practically insoluble in water; soluble in alcohol and in petroleum spirit (50 degrees to 70 degrees).

USNF 31: (Stearic Acid). A mixture of stearic acid and palmitic acid, the content of stearic acid being not less than 40%, and the sum of the two not less than 90%. Hard, white or faintly yellowish, somewhat glossy and crystalline solid, or white or yellowish-white powder, with a slight odour, suggesting tallow. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform and in ether.

USNF 31: (Purified Stearic Acid). It contains not less than 90% stearic acid and not less than 96% of stearic and palmitic acids. Congealing point 66 degrees to 69 degrees.

Profile

Stearic acid is used as a lubricant in making tablets and capsules. It is also used as an emulsifying and solubilising agent.

Stearyl Alcohol

Alcohol estearílico; Alcohol octadecílico; Alcohol Stearylicus; Alcool Stéarylique; Alkohol stearylowy; 1-Octadecanol; Octadecan-1-ol; Octadecyl Alcohol; Stearilo alkoholis; Stearilspirts; Stearylalkohol; Stéarylique, alcool; Stearyylialkoholi; Sztearil-alkohol; Стеариловый Спирт.

$C_{18}H_{38}O$=270.5
CAS — 112-92-5.
UNII — 2KR894H1Y.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Stearyl Alcohol). A mixture of solid alcohols; it contains not less than 95.0% of stearyl alcohol. White or almost white, unctuous flakes, granules, or mass. M.p. 57 degrees to 60 degrees. Practically insoluble in water; soluble in alcohol. When melted, it is miscible with fatty oils, with liquid paraffin, and with melted wool fat.

USNF 31: (Stearyl Alcohol). It contains not less than 90% of stearyl alcohol the remainder consisting chiefly of related alcohols. White unctuous flakes or granules with a faint characteristic odour. M.p. 55 degrees to 60 degrees. Insoluble in water; soluble in alcohol and in ether.

Uses

Stearyl alcohol is used to thicken topical and vaginal ointments and creams, and to increase their water-holding capacity; it has emollient and weak emulsifying properties. Stearyl alcohol is also used in oral solid dosage forms, including modified-release preparations.

Adverse Effects

Stearyl alcohol has been reported to cause hypersensitivity.

Hypersensitivity. Stearyl alcohol is usually considered to have a low potential for sensitisation although there have been isolated case reports of contact dermatitis from its use in topical products.[1-3]

1. Black H. Contact dermatitis from stearyl alcohol in Metosyn (fluocinonide) cream. *Contact Dermatitis* 1975; 1: 125.
2. de Berker D, *et al.* Contact sensitivity to the stearyl alcohol in Efudix™ cream (5-fluorouracil). *Contact Dermatitis* 1992; 26: 138.
3. Yesudian PD, King CM. Allergic contact dermatitis from stearyl alcohol in Efudix™ cream. *Contact Dermatitis* 2001; 45: 313–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: SFC Lotion†.

Multi-ingredient Preparations. *Arg.*: Calen†.

Stevioside

Esteviósido; Eupatorin; Rebaudin; Stevin; Steviosid; Stévioside; Steviosin; Steviozid; Steviozidas; Szteviozid; Стевиозид.

(4α)-β-D-Glucopyranosyl 13-[[2-*O*-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]kaur-16-en-18-oate.
$C_{38}H_{60}O_{18}$=804.9
CAS — 57817-89-7.
UNII — 0YON5MXJ9P.

Pharmacopoeias. In *Chin.*

Profile

Stevioside is a glycoside extracted from the leaves of yerba dulce, *Stevia rebaudiana* (Compositae). It has about 300 times the sweetness of sucrose and has been used as a sweetening agent in foods. Both the related glycoside rebaudioside A (rebiana), and an extract of the leaves of *Stevia rebaudiana*, which contains these and other glycosides, have been used similarly. The use of stevioside or stevia leaves as a sweetener has been banned in some countries due to concerns about genotoxicity and possible effects on fertility.

References.
1. Geuns JM. Stevioside. *Phytochemistry* 2003; 64: 913–21.
2. Wheeler A, *et al.* Pharmacokinetics of rebaudioside A and stevioside after single oral doses in healthy men. *Food Chem Toxicol* 2008; 46 (suppl 7): S54–S60.
3. Brusick DJ. A critical review of the genetic toxicity of steviol and steviol glycosides. *Food Chem Toxicol* 2008; 46 (suppl 7): S83–S91.
4. Chatsudthipong V, Muanprasat C. Stevioside and related compounds: therapeutic benefits beyond sweetness. *Pharmacol Ther* 2009; 121: 41–54.

Hypertension. The antihypertensive action of stevioside has been investigated. An oral dose of 250 mg three times daily was found to lower blood pressure in patients with mild to moderate hypertension,[1] and 500 mg three times daily decreased blood pressure and the incidence of left ventricular hypertrophy in patients with mild hypertension.[2] There appeared to be no clinically significant effects on blood pressure in a study in normotensive patients given rebaudioside A 1 g daily in divided doses.[3]

1. Chan P, *et al.* A double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension. *Br J Clin Pharmacol* 2000; 50: 215–20.
2. Hsieh M-H, *et al.* Efficacy and tolerability of oral stevioside in patients with mild essential hypertension: a two-year, randomized, placebo-controlled study. *Clin Ther* 2003; 25: 2797–2808.
3. Maki KC, *et al.* The hemodynamic effects of rebaudioside A in healthy adults with normal and low-normal blood pressure. *Food Chem Toxicol* 2008; 46 (suppl 7): S40–S46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Eco-Swett; Edulsan; Natural Sweet; Stevia Dulri.

Multi-ingredient Preparations. *Austral.*: Pe-Max; *Chile*: Nature Complex Reduct-Te; *Ukr.*: Sadifit (Садифит).

Succinic Acid

Acide succinique; Acido succinico; Ácido succínico; Amber Acid; Barnsteenzuur; Bärnstenssyra; Bernsteinsäure; Borostyánkősav; Dihydrofumaric Acid; Dzintarskābe; E363; Ethylenesuccinic Acid; Kwas bursztynowy; Kyselina jantarová; Meripihkahappo; Ravsyre; Янтарная Кислота; Янтарна киселина.

Butanedioic acid.
$C_4H_6O_4$=118.1
CAS — 110-15-6.
UNII — AB6MNQ6J6L.

Pharmacopoeias. In *USNF*.

USNF 31: (Succinic Acid). White, odourless crystals. Soluble in water, in alcohol, and in glycerol; freely soluble in boiling water.

Profile

Succinic acid is a naturally occurring organic acid used as a food additive (as is its sodium salt, p. 2620.1) and as a buffering agent in pharmaceuticals. It is also used as an intermediate in many industrial processes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: XLS; *Rus.*: Cytoflavin (Цитофлавин); Limontar (ЛИМОНТАР); Remaxol (Ремаксол); *Ukr.*: Cytoflavin (Цитофлавин); *USA*: VitaMed MD Iron 21/7.

Used as an adjunct in:. *Arg.*: Ferdromaco; *Fr.*: Inofer; *India*: Hematrine; *USA*: Chromagen FA; Chromagen Forte; Chromagen†; Multigen; Niferex; Repliva†; Trimagen†; Vitagen Advance.

Homoeopathic Preparations. *Canad.*: Ubicoenzyme; *Ger.*: Zitronensaurezyklus-Heel.

Sucrose Esters

E473 (sucrose esters of fatty acids); Sacarosa, ésteres de; Sacchari monopalmitas (sucrose monopalmitate); Sacchari monostearas (sucrose monostearate); Saccharose, monopalmitate de (sucrose monopalmitate); Saccharose, monostéarate de (sucrose monostearate); Sucroésteres; Эфиры Сахарозы.

Pharmacopoeias. *Eur.* (p. vii) and *USNF* include the palmitate and stearate esters.

Ph. Eur. 8: (Sucrose Monopalmitate). A mixture of sucrose monoesters, mainly sucrose monopalmitate, obtained by transesterification of palmitic acid methyl esters of vegetable origin with sucrose. It contains 55.0% monoesters, a maximum 40.0% diesters, and a maximum of 20.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

Ph. Eur. 8: (Sucrose Stearate). A mixture of sucrose esters, mainly sucrose stearate, obtained by transesterification of stearic acid methyl esters of vegetable origin with sucrose. Sucrose stearate type I contains a minimum 50.0% monoesters, a maximum 40.0% diesters, and a maximum of 25.0% for the sum of triesters and polyesters. Sucrose stearate type II contains 20.0 to 45.0% monoesters, 30.0 to 40.0% diesters, and a maximum of 30.0% for the sum of triesters and polyesters. Sucrose stearate type III contains 15.0 to 25.0% monoesters, 30.0 to 45.0% diesters, and 35.0 to 50.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

USNF 31: (Sucrose Palmitate). A mixture of sucrose monoesters, mainly sucrose monopalmitate, obtained by transesterification of palmitic acid methyl esters of vegetable origin with sucrose. It contains a minimum of 55.0%

monoesters, a maximum 40.0% diesters, and a maximum 20.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

USNF 31: (Sucrose Stearate). A mixture of sucrose esters, mainly sucrose stearate, obtained by transesterification of stearic acid methyl esters of vegetable origin with sucrose. Sucrose stearate type I contains a minimum 50.0% monoesters, a maximum 40.0% diesters, and a maximum of 25.0% for the sum of triesters and polyesters. Sucrose stearate type II contains 20.0 to 45.0% monoesters, 30.0 to 40.0% diesters, and a maximum of 30.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

Profile

Sucrose esters are polyalcohol ester nonionic surfactants (p. 2164.2) produced by esterification of 1 or more hydroxyl groups in sucrose with a fatty acid such as stearic or palmitic acid. Commercial sucrose esters are mixtures of the mono-, di-, and tri-esters of palmitic and stearic acids with sucrose; various grades are available. Sucrose esters are used as dispersing, emulsifying, and stabilising agents in food and cosmetic preparations.

Sucrose Octa-acetate

Octaacetate de Saccharose; Octaacetylsucrose; Sacarosa, octaacetato de; Sucrose, Octaacetate; Sucroseoctaacetat; Сахароза Октаацетат.

$C_{28}H_{38}O_{19}$=678.6

CAS — 126-14-7.

UNII — 07V5910571.

Pharmacopoeias. In *USNF*.

USNF 31: (Sucrose Octaacetate). A white, practically odourless, hygroscopic powder. M.p. not lower than 78 degrees. Soluble 1 in 1100 of water, 1 in 11 of alcohol, 1 in 0.3 of acetone, 1 in 0.5 of toluene, and 1 in 0.6 of benzene; very soluble in chloroform and in methyl alcohol; soluble in ether. Store in airtight containers.

Profile

Sucrose octa-acetate is an intensely bitter substance that has been used as an alcohol denaturant. It is also incorporated into preparations intended to deter nail biting.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Morde X†; *Switz.*: Bite-X.

Sulfated Castor Oil

Aceite de ricino sulfatado; Oil, Ricin, Sulphat; Oleum Ricini Sulphatum; Red Oil; Sulfonated Castor Oil; Sulphated Castor Oil; Turkey-red Oil; Ализариновое Масло; Сульфированное Касторовое Масло.

CAS — 8002-33-3.

Profile

Sulfated castor oil is a sulfated oil anionic surfactant (p. 2164.1) made by treating castor oil (p. 2472.1) with sulfuric acid then neutralising with sodium hydroxide. One of its main constituents is the sodium salt of sulfated ricinoleic acid. It is a detergent and wetting agent and has been used as a skin cleanser and emulsifier; it also has industrial and cosmetic applications.

Sulfated hydrogenated castor oil (hydroxystearin sulfate) has been used in the manufacture of hydrophilic ointment bases and other emulsions.

Other castor oil derivatives that have been used as anionic surfactants include sodium ricinoleate and potassium ricinoleate, which are alkali-metal soaps, and zinc ricinoleate (p. 2650.2), a metal soap.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Dermac.

Multi-ingredient Preparations. *Fr.*: Pyorex.

Sunset Yellow FCF

Amarillo anaranjado S; Amarillo ocaso FCF; CI Food Yellow 3; Colour Index No. 15985; Crelborange S; E110; FD & C Yellow No. 6; Gunsalmi Sarisi FCF; Jaune Orangé S; Jaune Soleil; Orange Yellow S; Para-orange; Paraoranssi; Zółcień Pomarańczowa FCF; Zonnegeel FCF; Жёлтый Солнечный Закат.

Disodium 6-hydroxy-5-(4-sulphonatophenylazo)naphthalene-2-sulphonate.

$C_{16}H_{10}N_2Na_2O_7S_2$=452.4

CAS — 2783-94-0.

UNII — H77VEI93A8.

Uses

Sunset yellow FCF is a synthetic azo dye used as a colouring agent in foods, medicines, and cosmetics. Sensitivity reactions have been reported.

Adverse Effects

Carcinogenicity. Although some evidence of carcinogenicity was found in early *animal* studies subsequent work failed to confirm these findings and in the UK sunset yellow FCF is considered suitable for use as a food colour.[1]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4*. London: HMSO, 1987.

Hypersensitivity. Hypersensitivity reactions including severe abdominal cramps,[1] Quincke's oedema,[2] and a severe skin reaction[3] have been recorded in individual patients receiving medication that was coloured with sunset yellow FCF.

1. Gross PA, *et al.* Additive allergy: allergic gastroenteritis due to yellow dye #6. *Ann Intern Med* 1989; 111: 87–8.
2. Lévesque H, *et al.* Reporting adverse drug reactions by proprietary name. *Lancet* 1991; 338: 393.
3. Rogkakou A, *et al.* Severe skin reaction due to excipients of an oral iron treatment. *Allergy* 2007; 62: 334–5.

Tamarind Polyose

E411; Tamarind Gum; Tamarind Gum Xyloglucan; Tamarind Kernel Gum; Tamarind Seed Polysaccharide; TSP.

CAS — 39386-78-2.

NOTE. The code E411 has been used for both tamarind seed flour and oat gum. The name Glyloid has been used as a trade mark for tamarind polyose.

Profile

Tamarind polyose is a polysaccharide extracted from the seed kernel of the tamarind tree, *Tamarindus indica* (see p. 1892.2). It is used as a gelling and thickening agent in foods and cosmetics, and industrially in the manufacture of textiles, paper, and gums. Pharmaceutically it has also been used as a tablet binder and as a component of modified-release tablets and mucoadhesive preparations. Tamarind polyose is also used in ophthalmic solutions for dry eye, and has been tried in formulations for prolonged ocular drug release.

References.

1. Rolando M, Valente C. Establishing the tolerability and performance of tamarind seed polysaccharide (TSP) in treating dry eye syndrome: results of a clinical study. *BMC Ophthalmol* 2007; 7: 5.
2. Kumar CS, Bhattacharya S. Tamarind seed: properties, processing and utilization. *Crit Rev Food Sci Nutr* 2008; 48: 1–20.
3. Gupta V, *et al.* Tamarind kernel gum: an upcoming natural polysaccharide. *Syst Rev Pharm* 2010; 1: 50–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Visine Professional†; Visine Tired Eyes†; *Ger.*: Visine Intensiv; Visine Mude; *Ital.*: Visine Intensive†; Visine Tired Eyes†.

Multi-ingredient Preparations. *UK*: Rohto Dry Eye Relief.

Tartrazine

CI Food Yellow 4; Colour Index No. 19140; E102; FD & C Yellow No. 5; Jaune Tartrique; Tartracina; Tartraslin; Tartratsiini; Tartrazin; Tartrazina; Tartrazinas; Tartrazol Yellow; Tartrazyna; Тартразин.

It consists mainly of trisodium 5-hydroxy-1-(4-sulphonatophenyl)-4-(4-sulphonatophenylazo)pyrazole-3-carboxylate.

$C_{16}H_9N_4Na_3O_9S_2$=534.4

CAS — 1934-21-0.

UNII — I753WB2F1M.

Uses

Tartrazine is a synthetic azo dye used as a colouring agent in foods, cosmetics, and medicines.

Adverse Effects

In addition to classical hypersensitivity reactions (see below), tartrazine has been considered to be implicated in the aggravation of hyperactive behaviour in children, as discussed under Colouring Agents, p. 2163.2.

Hypersensitivity. There have been many reports of reactions to tartrazine including angioedema, asthma, urticaria, and anaphylactic shock. Some of the reports have dealt with cross-sensitivity, especially with aspirin, although the connection with aspirin has been questioned.[1] A suggested incidence[2] of tartrazine sensitivity is 1 in 10 000. The mechanism of the reactions may not necessarily be immunological.[3]

In considering the reports of tartrazine sensitivity or intolerance the Food Advisory Committee in the UK[1] reported that similar evidence of intolerance might well be obtained for a variety of natural food ingredients if as many studies were conducted on them as on tartrazine. The Committee considered that tartrazine posed no more problems than other colours or food ingredients and recommended that the continued use of tartrazine in food was acceptable. However, use of tartrazine in medicines appears to be diminishing.

A systematic review[4] noted that there was no evidence that tartrazine makes asthma worse, nor did avoiding it make asthma any better.

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4*. London: HMSO, 1987.
2. Anonymous. Tartrazine: a yellow hazard. *Drug Ther Bull* 1980; 18: 53–5.
3. Murdoch RD, *et al.* Tartrazine induced histamine release in vivo in normal subjects. *J R Coll Physicians Lond* 1987; 21: 257–61.
4. Ardern K, Rana PSP. Tartrazine exclusion for allergic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 18/04/07).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Viticolor.

Tetrachloroethane

Acetylene Tetrachloride; Tetrachloroetan; Tetracloroetano; Tetracloroetano simétrico; Tetracloruro de acetileno; Тетрахлорэтан.

1,1,2,2-Tetrachloroethane.

$C_2H_2Cl_4$=167.8

CAS — 79-34-5.

Description. Tetrachloroethane is a colourless liquid with a chloroform-like odour. B.p. about 146 degrees. Wt per mL about 1.59 g. Store in airtight containers.

Uses

Tetrachloroethane is used as an industrial solvent.

Adverse Effects and Treatment

As for Carbon Tetrachloride, p. 2174.3. Tetrachloroethane is probably the most toxic of the chlorinated hydrocarbons. Poisoning can occur through percutaneous absorption as well as after ingestion or inhalation.

Handling. Suitable precautions should be taken to avoid skin contact with tetrachloroethane as it can penetrate skin and produce systemic toxicity.

Tetrachloroethylene

Czterochlorek etylenu; PERC; Perchloroethylene; Perchloroéthylène; Percloroetileno; Perkloretylen; Tetrachloooretheen; Tetrachlorethen; Tetrachlorethylen; Tetrachloroeten; Tetrachloroethene; Tétrachloroéthylène; Tetrachloroethylenum; Tetracloroetene; Tetracloroetilè; Tetracloroetileno; Тетрахлорэтен; Тетрахлорэтилен.

C_2Cl_4=165.8

CAS — 127-18-4.

UNII — T1904HH8SN.

Uses and Administration

Tetrachloroethylene is a chlorinated hydrocarbon widely used as a solvent in industry. It was formerly given orally as an anthelmintic, but has been superseded by equally effective and less toxic drugs.

Adverse Effects and Treatment

As for Carbon Tetrachloride, p. 2174.3. Symptoms, especially after ingestion, are less severe with tetrachloroethylene than with carbon tetrachloride.

The vapour or liquid may be irritating to skin or mucous membranes.

Tetrachloroethylene may be implicated in volatile substance abuse (see under Toluene, p. 2216.3). Depend-

ence may follow habitual inhalation of small quantities of tetrachloroethylene vapour.

References to adverse effects of tetrachloroethylene.

1. Bagnell PC, Ellenberger HA. Obstructive jaundice due to a chlorinated hydrocarbon in breast milk. *Can Med Assoc J* 1977; 117: 1047–8.
2. WHO. Tetrachloroethylene. *Environmental Health Criteria 31*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc31.htm (accessed 30/06/04)
3. WHO. Tetrachloroethylene health and safety guide. *IPCS Health and Safety Guide 10*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg010.htm (accessed 30/06/04)
4. Health and Safety Executive. Tetrachloroethylene (tetrachloroethene, perchloroethylene). *Toxicity Review 17*. London: HMSO, 1987.
5. Mutti A, *et al*. Nephropathies and exposure to perchloroethylene in dry-cleaners. *Lancet* 1992; 340: 189–93.

Pharmacokinetics

Tetrachloroethylene is slightly absorbed from the gastrointestinal tract; absorption is increased in the presence of alcohol and fats or oils. It is absorbed after inhalation and after direct contact with the skin. It is excreted unchanged in expired air; initial elimination is rapid but a proportion may be retained and excreted slowly.

Metabolites of tetrachloroethylene, mainly trichloroacetic acid, have been found in the urine.

Thaumatin *(BANJ)*

E957; Katemfe; Taumatin; Taumatina; Taumatyna; Thaumatine; Тауматин.

CAS — 53850-34-3.

UNII — KNC9Q0EE6G.

Profile

Thaumatin is a protein extracted from the fruit of *Thaumatococcus daniellii* (Marantaceae). It is a mixture of polypeptides, mainly thaumatin I and thaumatin II, each consisting of 207 amino acid residues and having a molecular weight of about 22 000. The amino-acid range excludes histidine. Thaumatin is an odourless, cream-coloured powder with an intensely sweet taste. The sweetness builds up gradually but persists for up to an hour, and has 2000 to 3000 times the sweetness of sucrose. It is approved as a sweetener and flavour modifier in foods, beverages, and pharmaceuticals.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Talin.

Theobroma

Cacao en polvo; Cacao or Cocoa Powder; Chocolate; Theobroma; Theobrom.; Kakao.

ATC Herb — HA05BA5004 (Theobroma cacao: seed).

UNII — D9108TZ9KG.

Pharmacopoeias. In *USNF*.

USNF 31: (Chocolate). A powder prepared from the roasted, cured kernels of the ripe seed of *Theobroma cacao* (Sterculiaceae).

Theobroma Oil

Beurre de cacao; Burro di cacao; Butyrum Cacao; Cacao Butter; Cacao Oleum; Cacaoboter; Cocoa Butter; Kaakaovoi; Kakaobutter; Kakaofett; Kakaosmör; Kakaosmør; Kakaóvaj; Kakaové máslo; Kakaový olej; Manteca de cacao; Manteiga de Cacau; Masło kakaowe; Ol. Theobrom.; Olej kakaowy; Oleum Cacao; Oleum Theobromatis; Tłuszcz kakaowy; Kakao-Macno; Macno Kakao.

CAS — 8002-31-1.

UNII — 512OYT1CRR.

Pharmacopoeias. In *Br., Fr., Ger., Jpn*, and *Pol*. Also in *USNF*.

BP 2014: (Theobroma Oil). The solid fat obtained from the roasted seeds of *Theobroma cacao*. A yellowish-white, somewhat brittle, solid fat, with a slight odour of cocoa. M.p. 31 degrees to 34 degrees. Slightly soluble in alcohol; freely soluble in chloroform, in ether, and in petroleum spirit (boiling range, 40 degrees to 60 degrees). Store at a temperature not exceeding 25 degrees.

USNF 31: (Cocoa Butter). A fat obtained from the seeds of *Theobroma cacao* (Sterculiaceae). It is a yellowish-white, usually brittle solid with a faint agreeable odour. M.p. 31 degrees to 35 degrees. Slightly soluble in alcohol; soluble in boiling dehydrated alcohol; freely soluble in chloroform and in ether.

Uses

Theobroma is used as a flavoured basis for tablets and lozenges. Theobroma oil is used as a basis for suppositories. If it is heated to more than 36 degrees during preparation the solidification point will be appreciably lowered due to the formation of metastable states; this leads to subsequent difficulty in setting. Theobroma oil is a major ingredient of chocolate.

Precautions

Breast feeding. The latest available guidance from the American Academy of Pediatrics[1] stated that irritability or increased bowel activity have been reported in infants whose mothers ate excessive amounts of chocolate (16 ounces (about 450 g) or more daily).

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 08/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Asthmatee EF-EM-ES; *Braz.*: Pomaderme; *Chile*: Cellenergy; *Fr.*: Amana Cellium; *India*: Aloat NC; *Malaysia*: Palmer's Cocoa Butter Formula Nappy Rash Ointment; Palmer's Cocoa Butter Formula Nursing Cream; Palmer's Cocoa Butter Formula Scar Serum; Palmer's Cocoa Butter Formula; *Singapore*: Rosken Skin Repair High Potency.

Pharmacopoeial Preparations

USNF 31: Chocolate Syrup.

Toluene

Fenilmetano; Metacida; Methylbenzene; Metilbenceno; Phenylmethane; Toluè; Tolueen; Tolueeni; Toluen; Toluenas; Toluène; Tolueno; Toluol; Toluole; Toluols; Tonyon; Тонуен.

C_7H_8=92.14

CAS — 108-88-3.

UNII — 3FPU23BG52.

Description. Toluene is a colourless, volatile, flammable liquid with a characteristic odour. Wt per mL about 0.87 g. B.p. about 111 degrees. Store in airtight containers.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of toluene:

Tolley; Tolly; Tooly.

Uses

Toluene is widely used as an industrial solvent.

Adverse Effects, Treatment, and Precautions

Toluene has similar acute toxicity to benzene (p. 2171.2) but is a less serious industrial hazard. Adverse effects are treated similarly to benzene. It is a common constituent of adhesives and is frequently implicated in volatile substance abuse (below). Commercial toluene may contain benzene, and this may perhaps influence the pattern of adverse effects. In addition to acute toxic effects, toluene abuse has been associated with damage to the nervous system, kidneys, liver, heart, and lungs (see below). Chronic poisoning caused by occupational exposure to toluene has resulted mainly in nervous system disorders.

Reviews.

1. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
2. WHO. Toluene. *Environmental Health Criteria 52*. Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc52.htm (accessed 30/06/04)
3. Health and Safety Executive. Toluene. *Toxicity Review 20*. London: HMSO, 1989.
4. IARC/WHO. Toluene. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; 71: 829–64. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

The non-neurological toxicity after volatile substance abuse has been reviewed.[1] Chronic toluene abuse may result in damage to the *kidneys*; renal tubular acidosis and glomerulonephritis have been described, although evidence for the latter is only circumstantial. Renal tubular acidosis has been regarded as reversible; however, there are reports suggesting that damage to renal tubules is permanent.

The few reports linking chronic toluene abuse with *liver* damage cover hepatomegaly and hepatorenal failure. Effects on the *heart* are usually acute; sudden death has resulted from ventricular arrhythmias. Chronic myocarditis with fibrosis has been reported. Chronic toluene inhalation can cause damage to the *lungs*. Autopsies in a few patients have shown changes indicative of emphysema.

Nervous system toxicity has also been reviewed.[2-5] Cerebellar dysfunction has occurred after toluene abuse; an acute intoxication phase, which usually subsides within weeks of abstinence, is followed by a chronic phase which may be permanent. Diffuse CNS disease such as encephalopathy, dementia, and multifocal brain injury may also develop. An association between toluene abuse and peripheral neuropathy has not been confirmed; muscle weakness may be a result of electrolyte and fluid disturbances. Choreoathetosis, epilepsy, and optic atrophy with anosmia and deafness have been reported after toluene abuse. Some of these neurological effects, particularly cerebellar effects and diffuse CNS disease have also occurred after occupational exposure to toluene.

Some studies have noted an excess mortality from motor neurone diseases among leather workers,[6] although this has not been confirmed by others.[7] Occupational exposure to solvents has been postulated as the cause.[8] Of the many agents currently used in leather work, those with known or probable neurotoxic effects are *n*-hexane, methyl butyl ketone, toluene, and methyl ethyl ketone. Ethyl acetate is commonly used but has no recognised neurological adverse effects.[6] A Swedish study of workers in a range of occupations has found some support for an increased risk of amyotrophic lateral sclerosis after occupational exposure to solvents, probably toluene and petrol.[8] Another Swedish study found an association between multiple sclerosis and occupational exposure to solvents, especially white spirit and petrol.[8]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; 8: 301–6.
2. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; 8: 293–300.
3. White RF, Proctor SP. Solvents and neurotoxicity. *Lancet* 1997; 349: 1239–43.
4. Pilley CM, *et al*. The effects of toluene on the central nervous system. *J Neuropathol Exp Neurol* 2004; 63: 1–12.
5. Yücel M, *et al*. Toluene misuse and long-term harms: a systematic review of the neuropsychological and neuroimaging literature. *Neurosci Biobehav Rev* 2008; 32: 910–26.
6. Hawkes CH, *et al*. Motoneuron disease: a disorder secondary to solvent exposure? *Lancet* 1989; i: 73–6.
7. Martyn CN. Motoneuron disease and exposure to solvents. *Lancet* 1989; i: 394.
8. Gunnarsson L-G, Lindberg G. Amyotrophic lateral sclerosis in Sweden 1970-83 and solvent exposure. *Lancet* 1989; i: 958.

Abuse. Since they are volatile liquids and have CNS effects many organic solvents, including toluene, are implicated in volatile substance abuse. Clinical features of intoxication are similar to those of alcohol intoxication, with initial CNS stimulation followed by CNS depression, which may progress to delirium, convulsions, coma, and death. Sudden death due to cardiac arrhythmias has also been reported.

References.

1. Proceedings of a meeting on substance abuse. *Hum Toxicol* 1989; 8: 253–334.
2. Ashton CH. Solvent abuse. *BMJ* 1990; 300: 135–6.
3. Brouette T, Anton R. Clinical review of inhalants. *Am J Addict* 2001; 10: 79–94.

Handling. Suitable precautions should be taken to avoid skin contact with toluene as it can penetrate skin and produce systemic toxicity.

Pregnancy. Retrospective surveys of pregnancies in mothers with a history of solvent abuse suggested that toluene abuse during pregnancy can cause preterm delivery and perinatal death. It was suggested that toluene may be teratogenic as intra-uterine exposure was associated with prenatal and postnatal growth retardation, microcephaly, impairment of mental development, and facial dysmorphia.[1-4] It is uncertain if these results can be extrapolated to cover occupational exposure. Although some studies of occupational exposure to solvents during pregnancy have suggested an association,[5,6] exposure is usually to several solvents[6] and there is little consistent evidence to link exposure to any particular one with spontaneous abortion, retarded fetal development, still-birth, or congenital malformation.[7]

1. Wilkins-Haug L, Gabow PA. Toluene abuse during pregnancy: obstetric complications and perinatal outcomes. *Obstet Gynecol* 1991; 77: 504–9.
2. Pearson MA, *et al*. Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 1994; 93: 211–15.
3. Arnold GL, *et al*. Toluene embryopathy: clinical delineation and developmental follow-up. *Pediatrics* 1994; 93: 216–20.
4. Bowen SE, Hannigan JH. Developmental toxicity of prenatal exposure to toluene. *AAPS J* 2006; 8: B419–B424.
5. McDonald JC, *et al*. Chemical exposures at work in early pregnancy and congenital defect: a case-referent study. *Br J Ind Med* 1987; 44: 527–33.
6. Khattak S, *et al*. Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. *JAMA* 1999; 281: 1106–9.
7. Scott A. *BMJ* 1992; 304: 369.

Pharmacokinetics

Toluene is absorbed after inhalation and ingestion, and to some extent through the skin. It is rapidly metabolised mainly by oxidation to benzoic acid which is excreted in the urine largely as the glycine conjugate hippuric acid; *o*-, *m*-, and *p*-cresol are minor urinary metabolites. Some unchanged toluene is excreted through the lungs.

Tonzonium Bromide *(rINN)*

Bromuro de tonzonio; NC-1264; NSC-5648; Thonzonium Bromide (USAN); Tonzonii Bromidum; Tonzonio, bromuro de; Tonzonium, Bromure de; Тонзония Бромид.
Hexadecyl[2-(N-p-methoxybenzyl-N-pyrimidin-2-ylamino)ethyl]dimethylammonium bromide.
$C_{32}H_{55}BrN_4O$=591.7
CAS — 553-08-2.
UNII — JI2B19ER0R.

Profile

Tonzonium bromide is a cationic surfactant. As an additive in ear drops and aerosol sprays it has been claimed to promote tissue contact by dispersion and penetration of cellular debris and exudate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA:* Coly-Mycin S Otic; Cortisporin-TC.

Tragacanth

Dragant; E413; Goma adragante; Goma Alcatira; Goma de tragacanto; Gomma adragante; Gomme Adragante; Gum Dragon; Gum Tragacanth; Kitre; Trag.; Tragacanta; Tragacantha; Tragacanto; Tragakanta; Tragakantas; Tragant; Traganth; Tragantmézga; Tragantti; Трагакантовая Камедь.
CAS — 9000-65-1.
ATC Herb — HA06AC5001 (Astragalus gummifer: mucilage).
UNII — 2944357O2O.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Tragacanth). The air-hardened gummy exudation flowing naturally or obtained by incision from the trunk and branches of *Astragalus gummifer* and some other species of *Astragalus* (Leguminosae) from western Asia. It occurs as thin, flattened, ribbon-like, white or pale yellow, translucent, horny strips. When reduced to a powder it forms a mucilaginous gel with about ten times its weight of water. Protect from light.

USNF 31: (Tragacanth). The dried gummy exudation from *Astragalus gummifer* or other Asiatic species of *Astragalus* (Leguminosae). It occurs as odourless, flattened, lamellated, frequently curved fragments or straight or spirally twisted linear pieces. It is white to weak yellow, translucent, and horny in texture. Powdered tragacanth is white to yellowish-white.

Uses

Tragacanth forms viscous solutions or gels with water, depending on the concentration. It is used in pharmaceutical manufacturing as a suspending agent and as an emulsifying agent. In dispensing aqueous preparations of tragacanth, the powdered tragacanth is first dispersed in a wetting agent, such as alcohol, to prevent agglomeration on the addition of water.

Tragacanth is also used for similar purposes in the food industry.

Adverse Effects

Hypersensitivity reactions, sometimes severe, have occurred rarely after the ingestion of products containing tragacanth. Contact dermatitis has been reported after the external use of tragacanth.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile:* Vaselina Emulsionada.

Trehalose *(BAN)*

Mycose; Trealosio; Trehaloosi; Trehalosa; α,α-Trehalose; Tréhalose; Trehalosum; Trehalóz; Trehaloza; Trehalóza; Tremalose; Трегалоза.
α-D-Glucopyranosyl-α-D-glucopyranoside.
$C_{12}H_{22}O_{11}$=342.3
CAS — 99-20-7 (anhydrous trehalose); 6138-23-4 (trehalose dihydrate).
UNII — B8WCK70T7I (trehalose); 7YIN7J07X4 (trehalose dihydrate).

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

Ph. Eur. 8: (Trehalose Dihydrate). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. pH of a 10% solution in water is 4.5 to 6.5.

USNF 31: (Trehalose). A white, odourless, non-hygroscopic crystalline powder. Soluble in water, the solubility increasing with increasing temperature; practically insoluble in dehydrated alcohol. pH of a 10% solution is 4.5 to 6.5. Store in airtight containers.

Profile

Trehalose is a naturally-occurring disaccharide used by various organisms as an energy source and to protect against the effects of freezing or drying. It is used as a filler and taste-masking agent in pharmaceutical formulations, and as a stabiliser for freeze-drying and lyophilisation. It is also used in cell cryopreservation and in the food and cosmetic industries.

References.

1. Richards AB, *et al.* Trehalose: a review of properties, history of use and human tolerance, and results of multiple safety studies. *Food Chem Toxicol* 2002; **40:** 871–98.

Tributyl Acetylcitrate

Acetyltributyl Citrate; Tributilo acetilcitratas; Tributylacetylcitrat; Tributyl-acetylcitrát; Tributyle, acétylcitrate de; Tributylis acetylcitras; Tributyyliasetyylisitraatti; Трибутилацетилцитрат.
Tributyl 2-(acetyloxy)propane-1,2,3-tricarboxylate.
$C_{20}H_{34}O_8$=402.5
CAS — 77-90-7.
UNII — 0ZBX0N59RZ.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Tributyl Acetylcitrate). A clear oily liquid. Immiscible with water; miscible with alcohol and with dichloromethane.

USNF 31: (Acetyltributyl Citrate). A clear, practically colourless, oily liquid. Insoluble in water; freely soluble in alcohol, in isopropyl alcohol, in acetone, and in toluene. Store in airtight containers.

Profile

Tributyl acetylcitrate is a plasticiser and flavour used in pharmaceutical manufacturing and in the food industry.

Tributyl Citrate

Butyl Citrate; Tributylu cytrynian; Трибутилцитрат.
Tributyl 2-hydroxy-1,2,3-propanetricarboxylate.
$C_{18}H_{32}O_7$=360.4
CAS — 77-94-1.
UNII — 827D5B1B6S.

Pharmacopoeias. In *USNF.*

USNF 31: (Tributyl Citrate). A clear, practically colourless, oily liquid. Insoluble in water; freely soluble in alcohol, in isopropyl alcohol, in acetone, and in toluene. Store in airtight containers.

Profile

Tributyl citrate is a citric acid ester used as a plasticiser in tablet and other pharmaceutical coatings.

Tri-*n*-butyl Phosphate

Fosfato de tributilo; Tributyl Phosphate; Tributyl-fosfát; Tributylis Phosphas; Tri-*n*-butylis Phosphas; Tri(*n*-butyl) phosphate; Tri-n-butilo fosfatas; Tri-n-butyle, phosphate de; Tri-n-butylfosfat; Tri-n-butylis Phosphas; Tri-n-butyylifosfaatti; Три-н-бутилфосфат.
Phosphoric acid tributyl ester.
$C_{12}H_{27}O_4P$=266.3
CAS — 126-73-8.
UNII — 95UAS8YAF5.

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

Ph. Eur. 8: (Tri-*n*-butyl Phosphate; Tributyl Phosphate BP 2014). A clear, colourless to pale yellow liquid. Slightly soluble in water; miscible with alcohol. Protect from light.

Profile

Tri-*n*-butyl phosphate is an organophosphate that is used as a solvent and plasticiser.

References.

1. WHO. Tri-*n*-butyl phosphate. *Environmental Health Criteria 112*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc112.htm (accessed 29/06/04)

Trichloroethane

Methylchloroform; Metilcloroformo; α-Trichloroethane; Tricloroetano; α-Tricloroetano; Triclorometilmetano; Трихлорэтан.
1,1,1-Trichloroethane.
$C_2H_3Cl_3$=133.4
CAS — 71-55-6.
UNII — 113C650IR1.

Description. Trichloroethane is a colourless, slightly hygroscopic liquid. Sp. gr. about 1.31. B.p. about 74 degrees. Practically insoluble in water; miscible with alcohol, with chloroform, and with ether. Non-flammable. Store in airtight containers.

Uses

Trichloroethane has wide applications as an industrial solvent. It is commonly used in dry cleaning, typewriter correction fluids, and as a solvent for plaster removal.

Adverse Effects and Treatment

Acute intoxication with trichloroethane may result in initial excitement followed by CNS depression with dizziness, drowsiness, headache, lightheadedness, and ataxia, progressing to coma and death from respiratory depression in severe cases. Death may also occur from ventricular arrhythmias. Fatalities have occurred after accidental exposure to high concentrations of trichloroethane in confined spaces. Trichloroethane is commonly used in dry cleaning, type correction fluids, and as a solvent for plaster removal and is frequently implicated in volatile substance abuse (see under Toluene, p. 2216.3).

Nausea, vomiting, and diarrhoea have been reported after ingestion. Trichloroethane is a mild irritant.

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures. Activated charcoal is unlikely to be of benefit after ingestion and gastric lavage is contra-indicated. Adrenaline and other sympathomimetics should be avoided because of the risk of precipitating cardiac arrhythmias.

Reviews.

1. Health and Safety Executive. 1,1,1-Trichloroethane. *Toxicity Review 9*. London: HMSO, 1984.
2. WHO. 1,1,1-Trichloroethane. *Environmental Health Criteria 136*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc136.htm (accessed 30/06/04)
3. IARC/WHO. 1,1,1,-Trichloroethane. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 881–903. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)
4. The Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of trichloroethane. *Int J Toxicol* 2008; **27** (suppl 4): 107–38.

Effects on the heart. Effects on the heart of trichloroethane abuse were considered usually to be acute, and sudden death from ventricular arrhythmias had occurred in abusers. There have, however, been a few cases of chronic cardiotoxicity after both abuse and occupational exposure.[1]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.

Effects on the liver. According to a brief review of non-neurological toxicity from volatile substance abuse,[1] there were no reports of damage to the liver after the abuse of trichloroethane. There was a report of hepatotoxicity after acute occupational exposure, but this might have been a hypersensitivity reaction. There was another report[2] of fatty liver disease in 4 patients with a history of occupational exposure to trichloroethane although there has been some debate over the validity of the association for 2 of these cases.[3,4] Chronic active hepatitis associated with trichloroethane exposure has since been reported.[5]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.
2. Hodgson MJ, *et al.* Liver disease associated with exposure to 1,1,1-trichloroethane. *Arch Intern Med* 1989; **149:** 1793–8.
3. Guzelian PS. 1,1,1-Trichloroethane and the liver. *Arch Intern Med* 1991; **151:** 2321–2.
4. Hodgson MJ, Vanthiel DH. 1,1,1-Trichloroethane and the liver. *Arch Intern Med* 1991; **151:** 2322 and 2325–6.
5. Croquet V, *et al.* Hépatite chronique active probablement induite par le 1,1,1-trichloroéthane. *Gastroenterol Clin Biol* 2003; **27:** 120–2.

Effects on the skin. Scleroderma has been reported[1] in 3 patients occupationally exposed to trichloroethylene and, in 2 cases, also to trichloroethane.

1. Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichlorethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; **67:** 263–4.

Pharmacokinetics

Trichloroethane is absorbed after inhalation and ingestion, and through intact skin. Small amounts are metabolised to trichloroethanol and trichloroacetic acid and excreted in the urine, but it is largely excreted unchanged through the lungs over a period of days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Zoff.

Triethyl Citrate

Citronensäuretriethylester; E1505; Triethyl citrát; Triëthylcitraat; Triethylcitrat; Triéthyle, citrate de; Triethyli Citras; Triethylis Citras; Trietil-citrát; Trietilo citratas; Trietilo, citrato de; Trietylcitrat; Trietyylisitraatti; Триэтилцитрат.
Triethyl 2-hydroxy-1,2,3-propanetricarboxylate.
$C_{12}H_{20}O_7$=276.3
CAS — 77-93-0.
UNII — 8Z96QXD6UM.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Triethyl Citrate). A clear, viscous, colourless or almost colourless, hygroscopic liquid. Soluble in water; miscible with alcohol; slightly soluble in fatty oils. Store in airtight containers.

USNF 31: (Triethyl Citrate). A practically colourless oily liquid. Soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Profile

Triethyl citrate is a plasticiser used in pharmaceutical manufacturing and in the food and cosmetics industries.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Uriage Desodorante Tri-Actif; *Fr.*: Spirial.

Triglycerol Diisostearate

Polyglyceryl-3 Diisostearate; Triglyceroldiisostearat; Triglyceroli Diisostearas; Triglyceryl Diisostearate.
CAS — 66082-42-6.
UNII — 46P231IQV8.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Triglycerol Diisostearate). A mixture of polyglycerol diesters of mainly isostearic acid, obtained by esterification of polyglycerol and isostearic acid. The polyglycerol consists mainly of triglycerol. A clear, yellowish, viscous liquid. Practically insoluble in water; miscible with alcohol and with fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Polyglyceryl 3 Diisostearate). A mixture of polyglycerol diesters of mainly isostearic acid, obtained by esterification of polyglycerol and isostearic acid. The polyglycerol consists mainly of triglycerol. A viscous liquid. Insoluble in water; soluble in alcohol, in dichloromethane, in liquid paraffin, and in vegetable oils. Store in airtight containers. Protect from heat, light, and moisture.

Profile

Triglycerol diisostearate is a polyalcohol (polyglycerol) ester nonionic surfactant (p. 2164.2) used as an emulsifier in topical preparations. Other polyglycerol esters are used similarly; polyglycerol polyricinoleate (E476) is used as an emulsifier in foods.

Turmeric

Açafrão-da-terra; CI Natural Yellow 3; Cúrcuma; Curcumae Rhizoma; Dažinė ciberžolė; Gurkemeie; Gurkemeje; Gurkmeja; Haldi; Indian Saffron; Kunir; Kunyit; Kurkuma; Mausterkurkuma; Ostryż Długi; Termeric; Zerdeçal; Куркума; Турмерик.
CAS — 458-37-7.
ATC Herb — HA05AW5005 (Curcuma longa: rhizome); HA03AW5020 (Curcuma longa: rhizome).
UNII — 856YO1Z64F.

Pharmacopoeias. In *Chin*, *Eur.* (see p. vii), and *Jpn*. Also in *US* which also includes a powdered form and a powdered extract.

Ph. Eur. 8: (Turmeric Rhizome; Curcumae Longae Rhizoma). The whole, cured (by boiling or steaming), dried rhizome of *Curcuma longa* (*Curcuma domestica*) with roots and outer surface removed. It contains not less than 25 mL/kg of essential oil and not less than 2.0% of dicinnamoyl methane derivatives expressed as curcumin, ($C_{21}H_{20}O_6$ = 368.4), both calculated with reference to the anhydrous drug. It has a spicy odour.

USP 36: (Turmeric). The dried rhizome of *Curcuma longa* (*C. domestica*) (Zingiberaceae). It is commonly known as Curcuma, Curcum, Haridra, and Indian Saffron. It contains not less than 3.0% of curcuminoids, calculated on the dried basis. Protect from light and moisture.

Uses

Turmeric is the dried rhizome of *Curcuma longa* (Zingiberaceae). Its main use is as a constituent of curry powders and other condiments, but it is also used as a yellow colouring agent in foods, either as the dried powder or as the oleoresin extract. It contains curcumin (p. 2180.1), which is the main colouring component, and other curcuminoids (p. 2489.3).

Turmeric and related Curcuma species, such as Javanese turmeric (*Curcuma xanthorrhiza*, p. 2636.2) and zedoary (*Curcuma zedoaria*) have been used in preparations indicated for biliary and gastrointestinal disorders and have also been promoted as anti-inflammatories. Turmeric oil has also been used.

Turmeric has been investigated for a wide range of pharmacological actions thought to be due to its curcuminoid content; curcumin and curcuminoid extracts have also been studied (see below).

Turmeric is a commonly used Ayurvedic medicine.

Reviews of the properties of turmeric and curcumin. See also reference to the properties of curcuminoids (p. 2489.3).

1. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. *Planta Med* 1991; 57: 1–7.
2. Grant KL, Schneider CD. Turmeric. *Am J Health-Syst Pharm* 2000; 57: 1121–2.
3. Ringman JM, *et al.* A potential role of the curry spice curcumin in Alzheimer's disease. *Curr Alzheimer Res* 2005; 2: 131–6.
4. Singh S, Khar A. Biological effects of curcumin and its role in cancer chemoprevention and therapy. *Anticancer Agents Med Chem* 2006; 6: 259–70.
5. Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. *Adv Exp Med Biol* 2007; 595: 105–25.
6. Sharma RA, *et al.* Pharmacokinetics and pharmacodynamics of curcumin. *Adv Exp Med Biol* 2007; 595: 453–70.
7. Scrimpakos AS, Sharma RA. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid Redox Signal* 2008; 10: 511–45.
8. Hatcher H, *et al.* Curcumin: from ancient medicine to current clinical trials. *Cell Mol Life Sci* 2008; 65: 1631–52.
9. Wongcharoen W, Phrommintikul A. The protective role of curcumin in cardiovascular diseases. *Int J Cardiol* 2009; 133: 145–51.
10. Bengmark S, *et al.* Plant-derived health: the effects of turmeric and curcuminoids. *Nutr Hosp* 2009; 24: 273–81.
11. Epstein J, *et al.* Curcumin as a therapeutic agent: the evidence from in vitro, animal and human studies. *Br J Nutr* 2010; 103: 1545–57.

Adverse Effects

Effects on the thyroid. There has been some concern about the safety of turmeric oleoresin after reports of adverse thyroid changes in *pigs*.[1,2]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FAAC/REP/4*. London: HMSO, 1987.
2. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 789* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_789.pdf (accessed 30/05/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Turmerik; *China*: Du Di (牡地); *Indon.*: Rheumakur†; *Pol.*: Solaren; *Spain*: Encimenal.

Multi-ingredient Preparations. *Austral.*: Arthriforte†; Boswellia Complex; Extralife Arthri-Care†; Extralife Liva-Care†; Joint Mobility†; PulmaCo; Vitanox; *Austria*: Apozema†; Spasmo Claim†; *Canad.*: Milk Thistle†; Optomega; Painease; *Cz.*: Cholagol; *Fr.*: Aromavital†; Cledist; Expuryl; Hepatoum; Silibiol; *Ger.*: Chol-Arbuz NF; Ventracid N†; *Hong Kong*: Procosa II†; *Hung.*: Antifront; Antifront; Cholagol; Munipyrin; *India*: Aglotus; Baknil; FN-T-Tus†; Healing Dust; *Indon.*: Aptivium Liver Support†; Cursil; Diapet; Entrodiar†; Fitodiar; Heparviton NF; Hepasil; Lanagogum; Lecur; Nutrijoint; Osimax; Ositin; Procur Plus; Proliva; Tripid; Vidoran Emulsion Rasa; Vidoran Plus; *Israel*: Coltect†; *Ital.*: Cinarepa; Cistefi; Clebolider†; Reumafort; *Jpn*: Cabe 2 New; Eki Cabe U; *Mex.*: Ifuchol; Procosa II; Rodan; *Philipp.*: Cogent db+; *Pol.*: Chelicur; Cholitol; *Rus.*: Cholagol (Холагол); Doktor Mom (Доктор Мом); Suprima-Broncho (Суприма-бронхо); Travisil (Трависил); *S.Afr.*: Lewensessens; *Singapore*: Arurex; Essentials†; Hepasil DTX†; Procosa II†; *Switz.*: Kernosan 24; *UK*: Arheumacare; BackOsamine; *Ukr.*: Antifront (Антифронт); Antifront (Антифронт); Artritosamin (Артритозамин); Bon-Apetit (Бон-Аппетит); Cholagol (Холагол); Choliver (Холивер)†; Doctor Cough (Доктор Кашель); Doktor Mom (Доктор Мом сироп); Hepahealth (Гепахелс); Memory Booster (Мемори Бустер); Olesan (Олесан)†; Vitrum Beauty Elite (Витрум Бьюти Элит).

Homoeopathic Preparations. *Fr.*: Billerol.

Tyloxapol *(BAN, USAN, rINN)*

Superinone; Tiloxapol; Tyloksapoli; Tyloxapolum; Тилоксапол.
CAS — 25301-02-4.
ATC — R05CA01.
ATC Vet — QR05CA01.
UNII — Y27PUL9H56.

Pharmacopoeias. In *US*.

USP 36: (Tyloxapol). A polymer of 4-(1,1,3,3-tetramethylbutyl)phenol with ethylene oxide and formaldehyde. A viscous amber liquid, sometimes slightly turbid, with a slight aromatic odour. Slowly but freely miscible with water; soluble in chloroform, in glacial acetic acid, in carbon disulfide, in carbon tetrachloride, in toluene, and in benzene. A 5% solution has a pH of 4.0 to 7.0. Tyloxapol should not be allowed to come into contact with metals. Store in airtight containers.

Uses and Administration

Tyloxapol is an alkyl aryl polyether alcohol nonionic surfactant (polymerised macrogol aryl ether; see p. 2164.2). It is used in solutions for cleansing contact lenses and artificial eyes. Aqueous solutions have been used for inhalation as a mucolytic for tenacious bronchopulmonary secretions. Tyloxapol has also been used as a vehicle for aerosol medication and for antibacterials given in irrigation solutions for pyogenic bone or joint infections.

Adverse Effects

Slight inflammation of the eyelids has been reported after prolonged use of aqueous inhalations of tyloxapol. It has been reported that occasional febrile reactions may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Enuclene; *Ger.*: Tacholiquin; *NZ*: Enuclene; *USA*: Enuclene.

Multi-ingredient Preparations. *Austral.*: Blink-N-Clean; *Malaysia*: Cationorm.

Vanilla

Baunilha; Semilla de vainilla; Vaina de vainilla; Vainilla; Vanile; Vanilj; Vanilja; Vanilje; Vanilka; Vanilla Beans; Vanilla Pods; Vanille; Vanilya; Wanilla; Ваниль; Ванилия.
UNII — Q74T35078H.

Pharmacopoeias. In *USNF*.

USNF 31: (Vanilla). The cured, full-grown, unripe fruit of *Vanilla planifolia*, often known in commerce as Mexican, Bourbon, or Madagascar vanilla, or of *V. tahitensis*, known in commerce as Tahitian vanilla (Orchidaceae). Vanilla that has become brittle should not be used. Store in airtight containers at a temperature not exceeding 8 degrees.

Profile

Vanilla is used as a flavour and in perfumery. However, the odour and flavour of vanilla are not entirely due to vanillin (see below) but depend on the presence of other aromatic substances. Preparations of vanilla have been used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Cyclotella.

Pharmacopoeial Preparations
USNF 31: Vanilla Tincture.

Vanillin

Vainillina; Vanillini; Vanilin; Vanillinas; Vanillic Aldehyde; Vanilline; Vanillinum; Wanilina; Ванилин.
4-Hydroxy-3-methoxybenzaldehyde.
$C_8H_8O_3$=152.1
CAS — 121-33-5.
UNII — CHI530446X.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet*. Also in *USNF*.

Ph. Eur. 8: (Vanillin). White or slightly yellowish crystalline needles or powder. M.p. 81 degrees to 84 degrees. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Vanillin). Fine, white to slightly yellow crystals, usually needle-like, having an odour and taste suggestive of vanilla. M.p. 81 degrees to 83 degrees. Soluble 1 in 100 of water at 25 degrees, 1 in 20 of water at 80 degrees, 1 in 20 of glycerol; freely soluble in alcohol, in chloroform, in ether, and in solutions of fixed alkali hydroxides. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Profile

Vanillin is used as a flavour and in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Pulmex Baby; Pulmex†; *Turk.*: Musilaks.

Pharmacopoeial Preparations
BP 2014: Tolu-flavour Solution.

Vegetable Carbon

Bitkisel Kömür; Carbon; Carbo; Carbón vegetal; Cendres végétales; Charbon végétal; Colour Index No. 77268:1; E153; Negro vegetal; Vegetable Black; Уголь Растительный.

UNII — 2KY1S0D0C4

NOTE. The name Carbon Black has also been used as a synonym for Channel Black, a colouring agent not used in food; care should be taken to avoid confusion between the two compounds.

Profile

Vegetable carbon, which consists essentially of finely divided carbon, is produced by the carbonisation of vegetable material such as peat or wood. It is used as a colouring agent for medicines, foodstuffs, and cosmetics.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Rus.*: Iris-Plus (*Ирис-Плюс*).

Vegetable Fatty Oils

Kasvirasvaöljyt; Olea Herbaria; Oljor, feta, vegetabiliska; Растительные Масла Жирные.

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

Ph. Eur. 8: (Vegetable Fatty Oils). Vegetable fatty oils are mainly solid or liquid triglycerides of fatty acids that may contain small amounts of other lipids such as waxes, free fatty acids, partial glycerides, or unsaponifiable matters. They are obtained from the seeds or fruits of plants by expression and/or solvent extraction, and may then be refined or hydrogenated with the addition of a suitable antoxidant if necessary. The following are defined:

- *virginoil*: the oil obtained from raw materials of special quality by mechanical procedures such as cold expression or centrifugation
- *refinedoil*: the oil obtained by expression and/or solvent extraction, and subsequently, either alkali refining (followed by bleaching and deodorisation) or physical refining
- *hydrogenatedoil*: an oil obtained by expression and/or solvent extraction, and subsequently, either alkali refining or physical refining, then possible bleaching, followed by drying, hydrogenation, and subsequently bleaching and deodorisation.

Only phosphoric acid and alkali refined oils may be used in the preparation of parenteral dosage forms.

Hydrogenated Vegetable Oil

Aceite vegetal hidrogenado.

Pharmacopoeias. In *Br.* *Jpn* allows under the title Hydrogenated Oil a product from fish, other animals or vegetables. Also in *USNF*.

BP 2014: (Hydrogenated Vegetable Oil). A mixture of triglycerides of fatty acids of vegetable origin. An almost white, fine powder at room temperature and a pale yellow, oily liquid above its m.p. of 57 degrees to 70 degrees. Practically insoluble in water; soluble in chloroform, in hot isopropyl alcohol, and in petroleum spirit. Store at a temperature of 8 degrees to 25 degrees.

USNF 31: (Hydrogenated Vegetable Oil). A mixture of triglycerides of fatty acids. Type 1 Hydrogenated Vegetable Oil occurs as a fine, white powder, beads, or small flakes; m. p. 57 degrees to 85 degrees. Type 2 Hydrogenated Vegetable Oil occurs as a plastic (semi-solid) or flakes, having a softer consistency than Type 1; m.p. 20 degrees to 50 degrees.

Insoluble in water; soluble in chloroform, in hot isopropyl alcohol, and in petroleum spirit. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Profile

Vegetable fatty oils are generally solid or liquid triglycerides of fatty acids that may contain small amounts of other lipids. They are obtained from the seeds or fruits of plants by expression and/or solvent extraction, and may then be refined or hydrogenated with the addition of a suitable antoxidant if necessary. They are fixed oils (expressed oils) and do not evaporate on warming as opposed to essential oils (ethereal oils, volatile oils), which evaporate readily and are usually obtained from their aromatic plant source by distillation. Some fixed vegetable oils are used to modify the consistency of ointments and for their emollient properties. They have also been used as vehicles for fat-soluble substances such as vitamins.

Hydrogenated vegetable oil is refined, bleached, hydrogenated, and deodorised vegetable oil stearins consisting mainly of the triglycerides of stearic and palmitic acids. It is used as a tablet lubricant and as an ointment or suppository basis.

White Spirit

Acquaragia; Lakibensiini; Lakkasprit; Siedegrenzbenzin; Stoddard Solvent; Terpentinersatz; Testbenzin; Trementina; Waschbenzin; Уайт-спирит.

CAS — 64742-82-1 (white spirit type 1); 64741-92-0 (white spirit type 2); 64742-48-9 (white spirit type 3); 64742-88-7 (white spirit type 0); 8052-41-3 (Stoddard solvent).
UNII — 37UN1I16R (Stoddard solvent).

Description. White spirit is a mixture of hydrocarbons available as a colourless liquid. Store in airtight containers.

Uses

White spirit is used as an industrial solvent. It is available in various grades. One grade available in the USA is known as Stoddard solvent.

Adverse Effects and Treatment

As for Kerosene, p. 2191.1.

References to the toxicity of white spirit.[1]

For discussion of neurotoxicity after occupational exposure to solvents including white spirit, see under Toluene, p. 2216.2.

1. WHO. Selected petroleum products. *Environmental Health Criteria 20.* Geneva: WHO, 1982. Available at: http://www.inchem.org/documents/ehc/ehc/ehc020.htm (accessed 30/06/04)

Wool Alcohols

Alcoholes Adipis Lanae; Alcoholes de lana; Alcoholes de lanolina; Alcoholia Lanae; Alcolanum; Alcools de graisse de laine; Alkoholy tuku z ovčí vlny; Gyapjúviaszalkoholok; Lanalcolum; Lanolin Alcohols; Ullfettalkoholer; Villa-alkoholit; Vilnų riebalų alkoholiai; Wollwachsalkohole; Wool Wax Alcohols; Спирты Шерстяного Жира.

CAS — 8027-33-6.
UNII — 884C3FA9HE

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Wool Alcohols). A mixture of sterols and higher aliphatic alcohols obtained from wool fat and containing not less than 30.0% of cholesterol. A suitable antoxidant may be added. A pale yellow to brownish-yellow, brittle mass becoming plastic on heating. M.p. not lower than 56 degrees. Practically insoluble in water; slightly soluble in alcohol (90%); soluble in boiling dehydrated alcohol, and in dichloromethane. Store in well-filled containers. Protect from light.

USNF 31: (Lanolin Alcohols). A mixture of sterols, aliphatic alcohols, and triterpenoid alcohols obtained by the hydrolysis of wool fat. It may contain not more than 0.1% of a suitable antoxidant. It is a hard, waxy amber solid with a characteristic odour. M.p. not below 56 degrees. Insoluble in water; slightly soluble in alcohol; freely soluble in chloroform, in ether, and in petroleum spirit. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Wool alcohols is incompatible with coal tar, ichthammol, resorcinol, and phenol.

Profile

Wool alcohols is an emulsifying agent and emulsion stabiliser used in the preparation of water-in-oil creams and ointments. It increases the water absorbing capacity of hydrocarbon mixtures; the addition of 5% of wool alcohols permits a threefold increase in the amount of water that can be incorporated in soft paraffin and such emulsions are not 'cracked' by the addition of weak acids.

It has an emollient action on the skin and is used in preparations for dry skin and dry eyes.

Derivatives of wool alcohols with similar uses include acetylated wool alcohols and ethoxylated wool alcohols.

Wool alcohols may cause hypersensitivity (but see also under Wool Fat, below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Refresh Lacri-Lube; *Fin.*: Lacri-Lube; *Ger.*: Coliquifilm; *Irl.*: Lacri-Lube; Oilatum Emollient; *Israel*: Adinol†; *Ital.*: Lacrilube; *NZ*: Lacrilube; *Switz.*: Coliquifilm; *UK*: Dermalo; Lacri-Lube; Oilatum Emollient; *USA*: Aquaphor Healing Ointment; DermaPhor; Hydrocerin; Hydrocerin; Refresh Lacri-Lube; Refresh PM.

Pharmacopoeial Preparations
BP 2014: Wool Alcohols Ointment.

Wool Fat

Adeps Lanae; Adeps lanae hydrogenatus (wool fat, hydrogenated); Anhydrous Lanolin; Cera Lanae; Graisse de laine; Graisse de laine hydrogénée (wool fat, hydrogenated); Graisse de Suint Purifiée; Gyapjúviasz; Lanoléine; Lanolin; Lanolina; Lanolina, anidra; Lanolinum; Purified Lanolin; Refined Wool Fat; Suarda; Tuk z ovčí vlny; Tuk z ovčí vlny hydrogenovaný (wool fat, hydrogenated); Ullfett; Villarasva; Vilnų riebalai; Wollfett; Wollwachs; Ланолин; Шерстяной Жир.

CAS — 8006-54-0.
UNII — 7EV65EAW6H

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include Hydrous Wool Fat which is prepared by the addition of water to wool fat.

Eur. also includes Hydrogenated Wool Fat.

US also includes Modified Lanolin.

Ph. Eur. 8: (Wool Fat). A purified, anhydrous, waxy material obtained from the wool of the sheep (*Ovis aries*). A suitable antioxidant may be added. A yellow, unctuous substance. When melted, it is a clear or almost clear, yellow liquid. Drop point 38 degrees to 44 degrees. 10 g absorbs not less than 20 mL of water. Practically insoluble in water; slightly soluble in boiling dehydrated alcohol; it forms an opalescent solution in petroleum spirit. Store at a temperature not exceeding 25 degrees.

Ph. Eur. 8: (Wool Fat, Hydrogenated; Adeps Lanae Hydrogenatus). A mixture of higher aliphatic alcohols and sterols obtained from the direct, high-pressure, high-temperature hydrogenation of anhydrous wool fat during which the esters and acids present are reduced to corresponding alcohols. A suitable antoxidant may be added. A white or pale yellow, unctuous substance. M.p. 45 degrees to 55 degrees. Practically insoluble in water; soluble in boiling dehydrated alcohol and in petroleum spirit. Store in well-filled containers. Protect from light.

Ph. Eur. 8: (Wool Fat, Hydrous; Adeps Lanae Cum Aqua). A mixture of 75% of wool fat and 25% of water. A suitable antoxidant may be added. A pale yellow, unctuous substance. Drop point 38 degrees to 44 degrees. Store at a temperature not exceeding 25 degrees.

USP 36: (Lanolin). A purified wax-like substance obtained from the wool of the sheep, *Ovis aries* (Bovidae). It is a yellow tenacious unctuous mass with a slight characteristic odour. Melting range 38 degrees to 44 degrees. It contains not more than 0.25% of water. It may contain not more than 0.02% of a suitable antoxidant. Insoluble in water, but mixes without separation with about twice its weight of water; sparingly soluble in cold alcohol; more soluble in hot alcohol; freely soluble in chloroform and in ether. Store at a temperature preferably between 15 degrees and 30 degrees.

USP 36: (Modified Lanolin). It is Lanolin that has been processed to reduce the contents of free lanolin alcohols and detergent and pesticide residues. It contains not more than 0.25% of water. It may contain not more than 0.02% of a suitable antoxidant. Store in airtight, preferably rust-proof, containers and preferably at a temperature of 15 degrees to 30 degrees.

Uses

Wool fat is used in the formulation of water-in-oil creams and ointments. When mixed with a suitable vegetable oil or with soft paraffin it gives emollient creams that penetrate the skin. It can absorb about 30% of water. Wool fat is also used in other topical, vaginal, rectal, and ophthalmic preparations.

Derivatives and modifications of wool fat include hydrogenated wool fat (hydrogenated lanolin), hydrous wool fat (hydrous lanolin), poloxyl lanolin (ethoxylated lanolin), isopropyl lanolate, lanolin oil, and lanolin wax.

Adverse Effects and Precautions

Wool fat can cause hypersensitivity reactions.

Hypersensitivity. Wool fat is widely regarded as a common sensitising agent, but the true extent of allergy to it is controversial.[1] Suspected sensitivity reactions have proved dif-

ficult to reproduce in skin patch testing.[2] The allergens are unknown but are thought to be in the alcoholic fraction. A retrospective study[3] of more than 24 000 patients with eczema who received skin patch testing found that sensitivity reactions to a standard patch reagent of wool alcohols 30% in soft paraffin were rare; an average of 1.7% of patients per year showed sensitivity.

1. Lee B, Warshaw E. Lanolin allergy: history, epidemiology, responsible allergens, and management. *Dermatitis* 2008; 19: 63–72.
2. Wolf R. The lanolin paradox. *Dermatology* 1996; 192: 198–202.
3. Wakelin SH, *et al.* A retrospective analysis of contact allergy to lanolin. *Br J Dermatol* 2001; 145: 28–31.

Pesticide residues. Concerns have been raised in the past about pesticide residues in wool fat,[1-3] because of the possible risk to breast-fed infants whose mothers were using wool fat-based nipple ointments. Official published standards such as Ph. Eur. and USP now include limits for pesticide levels in wool fat.

1. Copeland CA, *et al.* Pesticide residue in lanolin. *JAMA* 1989; 261: 242.
2. Cade PH. Pesticide in lanolin. *JAMA* 1989; 262: 613.
3. Copeland CA, Wagner SL. Pesticide in lanolin. *JAMA* 1989; 262: 613.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Lansinoh; *Canad.*: PureLan; *Ger.*: Oleo Tull: *India*: Nipcare; *S.Afr.*: Duratears; *Turk.*: Duratears; *UK*: Evolve Plus; *USA*: Lan-O-Smooth; Lansinoh.

Multi-ingredient Preparations. *Arg.*: Alcon Lagrimas; Crema Para Paspaduras†; Dr Selby; Ninderm; *Austral.*: Alpha Keri; Duratears; E45; Poly Visc; Soothe'n Heal†; *Austria*: Tiroler Steinol; *Belg.*: Duratears; Lacrytube; *Canad.*: A & D Ointment; Akwa Tears; Flexitol Heel Balm†; Huile de Bain Therapeutique; Lotion Lubrifiante Calmante Hydratante†; Optilube; Secol; Tears Naturale PM; *Chile*: Duratears; Lacri-Lube; Pasta Lassar; *Fr.*: Jouvence; *Ger.*: Sofra-Tull sine; Vita-POS; *Gr.*: Duratears; Fissan-Pate; *Hong Kong*: Duratears; *India*: Elure; *Indon.*: Yanthi Baby Oil†; *Israel*: Duratears; Kamil Blue; Lacrimol†; Pedisol†; Vita-POS; *Malaysia*: Balneum†; Duratears Naturale; Lacrilube; *Mex.*: Acuafil Ungena; *Neth.*: Duratears Z; *NZ*: Alpha Keri; BK; DP Lotion - HC; DP; Hydroderm; Oralife Peppermint; *Pol.*: E45; *Singapore*: Balneum; Duratears; Lacrilube†; *Spain*: Lubrifilm†; Pasta Lassar Imba; *Switz.*: Nasomed; *Thai.*: Duratears; *UK*: Alpha Keri; Hewletts†; Lubri-Tears†; Melrose; VitA-POS; *USA*: Akwa Tears†; Alpha Keri; Bodi Oil; Bottom Better†; Dermadrox; Dry Eyes; Duratears Naturale; Geri-Silk; Lacri-Gel; Lacri-Lube; Lansinoh Diaper Rash; Lantiseptic; LubriFresh PM; LubriTears; Paladin; Palomar E; Systane Nighttime; *Venez.*: Oleoderm.

Pharmacopoeial Preparations
BP 2014: Simple Eye Ointment; Simple Ointment.

Xanthan Gum

Corn Sugar Gum; E415; Goma de xantána; Gomma di xantano; Gomme xanthane; Guma ksantanowa; Ksantaanikumi; Ksantano lipai; Polysaccharide B 1459; Xantán gumi; Xantangummi; Xanthaangom; Xantham Gum; Xanthangummi; Xanthani gummi; Xanthanová klovatina; Ксантановая Гума; Ксантановая Камедь.

CAS — 11138-66-2.
UNII — TTV12P4NEE.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Xanthan Gum). A gum produced by fermentation of a carbohydrate with *Xanthomonas campestris* and purified. It is the sodium, potassium, or calcium salt of a high-molecular-weight polysaccharide containing D-glucose, mannose, and glucuronic acid. It also contains not less than 1.5% of pyruvic acid, calculated with reference to the dried substance. A white or yellowish-white, free-flowing powder. Soluble in water giving a highly viscous solution; practically insoluble in organic solvents. A 1% solution in water has a pH of 6.0 to 8.0.

USNF 31: (Xanthan Gum). A high-molecular-weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with *Xanthomonas campestris* and purified. It contains D-glucose, D-mannose, and D-glucuronic acid. It is prepared as the sodium, potassium, or calcium salt. A cream-coloured powder. Soluble in hot or cold water. Its solutions are neutral to litmus.

Profile

Xanthan gum is used in pharmaceutical manufacturing as a suspending, stabilising, thickening, and emulsifying agent. It is also used similarly in the food industry.

Suspensions of crushed tablets or insoluble powders made with xanthan gum were reported to be preferable to those made with tragacanth.[1]

The stability was generally good and only a small number of drugs had been found to be incompatible (amitriptyline, tamoxifen, and verapamil).[1] For extemporaneous dispensing, a 1% solution of xanthan gum with hydroxybenzoate, prepared in advance, was diluted to 0.5% with water when preparing the suspension.

Xanthan gum was found to be a suitable suspending vehicle for delivering antispasmodics topically along the length of the oesophagus in patients with oesophageal spasm.[2] Coagulation of the gum had occurred when it was used for suspensions of certain film-coated tablets.

1. Anonymous. "Extremely useful" new suspending agent. *Pharm J* 1986; 237: 665.
2. Evans BK, Fenton-May V. Keltrol. *Pharm J* 1986; 237: 736–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Ronfnyl.

Multi-ingredient Preparations. *Fr.*: Cyamox; Cyamox; Herpclair; *Ital.*: Noremifa; Panamir; Resource Gelificata†; Xanternet; *Switz.*: Prevalin; *Turk.*: Xialine; *USA*: Mimyx†.

Pharmacopoeial Preparations
USNF 31: Xanthan Gum Solution.

Xylene

Dimethylbenzene; Dimetilbenceno; Ksilenas; Ksilols; Ksylen; Xilè; Xilene; Xileno; Xyleen; Xylen; Xylène; Xylol; Xylole; Ксилол.

C_8H_{10}=106.2
CAS — 1330-20-7; 108-38-3 (m-xylene); 95-47-6 (o-xylene); 106-42-3 (p-xylene).
UNII — DB56J1047R (xylene mixed); O9XS864HTE (m-xylene); Z2474E14QP (o-xylene); 6WAC1O477V (p-xylene).

Description. Xylene is a mixture of the *o-*, *m-*, and *p-*isomers in which the *m*-isomer predominates. It is a colourless, volatile, flammable liquid. Wt per mL about 0.86 g. B.p. about 138 degrees to 142 degrees. Store in airtight containers.

Uses

Xylene is used as an industrial and pharmaceutical solvent and in preparations to dissolve ear wax.

Adverse Effects, Treatment, and Precautions

The acute toxicity of xylene is similar to that of benzene (p. 2171.2) but is less marked. Adverse effects are treated similarly to benzene.

Xylene has been implicated in volatile substance abuse (see under Toluene, p. 2216.3). Commercial xylene may contain benzene, and this may perhaps influence the pattern of adverse effects.

Xylene should not be used to dissolve ear wax if the tympanic membrane is perforated.

References.

1. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
2. Health and Safety Executive. Xylenes. *Toxicity Review 26*. London: HMSO, 1992.
3. WHO. Xylenes. *Environmental Health Criteria 190*. Geneva: WHO, 1997. Available at: http://www.inchem.org/documents/ehc/ehc/ehc190.htm (accessed 30/06/04)
4. IARC/WHO. Xylenes. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; 71: 1189–1208. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

Effects on the eyes. Eye injuries due to accidental contact with paints containing xylene have been reported.[1] The injuries resembled alkali burns and were treated in a similar manner. Xylene-induced keratopathy has been reviewed.[2]

1. Ansari EA. Ocular injury with xylene - a report of two cases. *Hum Exp Toxicol* 1997; 16: 273–5.
2. Trujillo P, *et al.* Xylene keratopathy: a case report and review of the literature. *Cornea* 2003; 22: 88–90.

Effects on the nervous system. References.

1. Arthur LJH, Curnock DA. Xylene-induced epilepsy following innocent glue sniffing. *BMJ* 1982; 284: 1787.
2. Roberts FP, *et al.* Near-pure xylene causing reversible neuropsychiatric disturbance. *Lancet* 1988; ii: 273.
3. Draper TH, Samiou DE. Auditory neuropathy in a patient exposed to xylene: case report. *J Laryngol Otol* 2009; 123: 462–5.

Handling. Suitable precautions should be taken to avoid skin contact with xylene as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Xylene is absorbed after inhalation, ingestion, and to some extent through the skin. It is rapidly metabolised by oxidation to the corresponding *o-*, *m-*, or *p*-methylbenzoic (toluic) acids and excreted in the urine largely as the glycine conjugate, methylhippuric acid (toluric acid). Xylenols are minor metabolites and are excreted in the urine as the glucuronide and sulfate conjugates. Some unchanged xylene is excreted through the lungs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Cerulyx; *Fr.*: Cerulyse; *Ital.*: Cerulisina.

Xylitol (BAN)

E967; Ksilitolis; Ksylitol; Ksylitoli; *meso*-Xylitol; Xilit; Xilitol; Xylit; Xylitolum; Ксилит.

$C_5H_{12}O_5$=152.1
CAS — 87-99-0 (xylitol); 16277-71-7 (D-xylitol).
UNII — VCQ006KQ1E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Xylitol). A white or almost white crystalline powder or crystals. M.p. 92 degrees to 96 degrees. Very soluble in water; sparingly soluble in alcohol.

USNF 31: (Xylitol). White crystals or crystalline powder. Crystalline xylitol has a melting range between 92 degrees and 96 degrees. It has a sweet taste and produces a cooling sensation in the mouth. Soluble 1 in about 0.65 of water; sparingly soluble in alcohol.

Uses and Administration

Xylitol is a polyhydric alcohol (polyol) related to the pentose sugar, xylose (p. 2649.2). It is similar in sweetness to sucrose and is used as a bulk sweetener in foods and as a sweetener or excipient in pharmaceuticals. Xylitol is also used as a sweetening agent in sugar-free preparations as it is noncariogenic and is less likely to cause dental caries than sucrose. It may also have a role in the prevention of dental caries (see below). It was formerly considered as a substitute for glucose in intravenous nutrition but such use has generally been abandoned due to adverse effects.

Dental caries. Preparations containing xylitol appear to have a useful role in the prevention of dental caries (p. 192.3),[1-6] both by stimulating salivation and by direct effects. They may also aid dental remineralisation.[7]

1. Edgar WM. Sugar substitutes, chewing gum and dental caries—a review. *Br Dent J* 1998; 184: 29–32.
2. Gales MA, Nguyen T-M. Sorbitol compared with xylitol in prevention of dental caries. *Ann Pharmacother* 2000; 34: 98–100.
3. Maguire A, Rugg-Gunn AJ. Xylitol and caries prevention—is it a magic bullet? *Br Dent J* 2003; 194: 429–36.
4. van Loveren C. Sugar alcohols: what is the evidence for caries-preventive and caries-therapeutic effects? *Caries Res* 2004; 38: 286–93.
5. Burt BA. The use of sorbitol- and xylitol-sweetened chewing gum in caries control. *J Am Dent Assoc* 2006; 137: 190–6. Correction. *ibid.*; 447.
6. Milgrom P, *et al.* Xylitol pediatric topical oral syrup to prevent dental caries: a double-blind randomized clinical trial of efficacy. *Arch Pediatr Adolesc Med* 2009; 163: 601–7.
7. Mäkinen KK. Sugar alcohols, caries incidence, and remineralization of caries lesions: a literature review. *Int J Dent* 2010; 2010: 981072.

Otitis media. There is some evidence that xylitol chewing gum[1,2] or syrup,[2,3] used 5 times daily, has a preventative effect against acute otitis media (p. 195.2) in children. However, another study[4] found that xylitol had no effect when given only during acute respiratory-tract infections, and use of a higher dose 3 times daily also proved ineffective.[5] A systematic review[6] concluded that use of xylitol was of benefit but that further study was needed to establish more convenient dosage regimens.

1. Uhari M, *et al.* Xylitol chewing gum in prevention of acute otitis media: double blind randomised trial. *BMJ* 1996; 313: 1180–4.
2. Uhari M, *et al.* A novel use of xylitol sugar in preventing acute otitis media. *Pediatrics* 1998; 102: 879–84.
3. Uhari M, *et al.* Xylitol in preventing acute otitis media. *Vaccine* 2001; 19: S144–S147.
4. Tapiainen T, *et al.* Xylitol administered only during respiratory infections failed to prevent acute otitis media. Abstract: *Pediatrics* 2002; 109: 302. Full version: http://pediatrics.aappublications.org/cgi/reprint/109/2/e19 (accessed 23/08/10)
5. Hautalahti O, *et al.* Failure of xylitol given three times a day for preventing acute otitis media. *Pediatr Infect Dis J* 2007; 26: 423–7.
6. Danhauer JL, *et al.* Xylitol as a prophylaxis for acute otitis media: systematic review. *Int J Audiol* 2010; 49: 754–61.

Adverse Effects

Large amounts of xylitol taken orally may cause diarrhoea and flatulence. Hyperoxaluria, which can occur with intravenous infusion, is unlikely after oral use. Hyperuricaemia, changes in liver-function tests, and acidosis (including lactic acidosis) have occurred after intravenous infusion.

Hypersensitivity. A report of oral erosions caused by contact hypersensitivity to xylitol-containing chewing gum.[1]

1. Hanakawa Y, *et al.* Xylitol as a causative agent of oral erosive eczema. *Br J Dermatol* 2005; 152: 821–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Trident; *China*: De Li Er Xin (得力尔欣); Ya Qing Ning (雅清宁); *Ger.*: Xylit†; *Philipp.*: Xylogel; *USA*: XyliMelts.

Multi-ingredient Preparations. *Arg.*: Bucal Hyper Sensitive; Bucal Tac Whitening Gel; Bmoform Total; Esmedent; Fluorogel 2001 para Dientes Sensibles; Fluorogel 2001; Minamint; Periobacter; Periodent; Solucion Oral; Tac Fluor; *Chile*: Oralgene; *Ger.*: GX; InfectoGripp; Infesol XE; Parentamin X-E†; Periplasmal XE; Saliva natura; Saseem; *India*: Hermin; Klidodent; *Indon.*: Aminofusin L; Comafusin Hepar; Intrafusin SX-E; Precopar; Trifluid; *Jpn*: Amizet XB; Proteamin; Trifluid; Triparen; *Mex.*: Dentsiblen†; Fluoxytil†; Periodentyl; Perioxidin†; *Neth.*: Saliva Orthana; *Philipp.*: Xylorinse; *UK*: AS Saliva Orthana; AS Saliva Orthana; Biotene Oralbalance; Saliva Natura; *Ukr.*: Glauxyl (Глюксил)†; Gluxyl (Глюксил); Infesol 40 (Инфесол 40); Xylat (Ксилат); *USA*: Optimoist; SalivaSure.

Yellow 2G

107; Acid Light Yellow 2G; Acid Yellow 17; Amarillo 2G; CI Food Yellow 5; Colour Index No. 18965; Geel 2G; Geltonasis 2G; Gul 2G; Jaune 2G; Zolcien 2G; Xemuii 2G.

Disodium 2,5-dichloro-4-[5-hydroxy-3-methyl-4-(4-sulphonatophenylazo)pyrazol-1-yl]benzenesulphonate.

$C_{16}H_{10}Cl_2N_4Na_2O_8S_2$=551.3

CAS — 6359-98-4.

Profile

Yellow 2G is a synthetic azo dye used as a colouring agent in cosmetics.

Zein

Zeina; Зеин

CAS — 9010-66-6 (zeins).

UNII — 6ON30BTHNN.

Pharmacopoeias. In *Chin.* Also in *USNF*.

USNF 31: (Zein). A prolamine derived from corn, *Zea mays* (Gramineae). A white to yellow powder. Insoluble in water and in acetone; readily soluble in acetone-water mixtures between the limits of 60% and 80% of acetone by volume; soluble in aqueous alcohols, in ethoxyethanol, in glycols, in furfuryl alcohol, in tetrahydrofurfuryl alcohol, and in aqueous alkaline solutions of pH 11.5 and above; insoluble in all anhydrous alcohols except methyl alcohol.

Profile

Zein is used as a tablet binder and coating agent for pharmaceutical preparations and foodstuffs. It has been used as a substitute for shellac.

Zinc Stearate

Cinko stearatas; Cink-sztearát; Cynku stearynian; Estearato de Zinc; Sinkkistearaatti; Stearan zinečnatý; Zinc stearate de; Zinci stearas; Zinkstearat; Стеарат Цинка.

Zinc octadecanoate.

CAS — 4991-47-3 (zinc palmitate); 557-05-1 (zinc stearate).

UNII — H92E6QA4FV.

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

Ph. Eur. 8: (Zinc Stearate). Zinc stearate [$(C_{17}H_{35}CO_2)_2Zn$ = 632.3] may contain varying proportions of zinc palmitate [$(C_{15}H_{31}CO_2)_2Zn$ = 576.2] and zinc oleate [$(C_{17}H_{33}CO_2)_2Zn$ = 628.3]. A light, white or almost white, amorphous powder, free from gritty particles. Practically insoluble in water and in dehydrated alcohol.

USP 36: (Zinc Stearate). A compound of zinc with a mixture of solid organic acids obtained from fats and consisting mainly of variable proportions of zinc stearate [$(C_{17}H_{35}CO_2)_2Zn$ = 632.3] and zinc palmitate [$(C_{15}H_{31}CO_2)_2Zn$ = 576.2]. A fine, white, bulky powder, free from grittiness, with a faint characteristic odour. Insoluble in water, in alcohol, and in ether.

Uses

Zinc stearate is a metal soap anionic surfactant (p. 2164.1). It is used as a lubricant for granules in the manufacture of tablets and capsules and also has industrial and cosmetic applications. It has been used as a soothing and protective application in the treatment of skin inflammation and may be used as a powder or as a cream.

Adverse Effects

Zinc stearate inhalation has caused fatal pneumonitis, particularly in infants.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Prurisedan; *Israel*: Acti Talc *Ital.*: Steril Zeta; *Switz.*: Hydrocortisone compositum†; *Thai.*: Banocin; *UK*: Simpsons; *Venez.*: Borocanfor.

Pharmacopoeial Preparations

USP 36: Compound Clioquinol Topical Powder.

Radiopharmaceuticals

Radioactive compounds are used in nuclear medicine as sources of radiation for radiotherapy and for diagnostic purposes. They have many uses in research and industry.

Radiopharmaceuticals are medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose. Usually they consist of a cold kit, a non-radioactive chemical component or drug, coupled with a radionuclide. The chemical component or drug localises in the target area and the radionuclide emits radiation. Some radiopharmaceuticals are designed to act as a signal generator, providing relatively harmless emissions to provide physiological imaging for diagnosis (tracer procedures or studies), whereas others are therapeutic in nature and intentionally harmful to targeted tissue, in order to destroy aberrant or cancerous cells. Radiopharmaceuticals are prepared in many forms, including intravenous injections, gases, aerosols, oral solutions, and capsules.

The aim of this chapter is to provide background information on the radionuclides that are used as radiopharmaceuticals. Care is required in the preparation, handling, use, and disposal of these compounds; they are thus best dealt with by those with suitable experience and training.

Atomic Structure

The classical model of the atom represents it as a central positively charged nucleus around which negatively charged electrons revolve in orbits. The electrons are arranged round the atomic nucleus in a series of 'shells' in each of which is a limited number of orbits. Although now superseded in physics, this model remains useful as a convenient simplification in chemistry and radiochemistry.

The nucleus consists of 2 main kinds of particles: protons, each of unit positive charge, and neutrons, which are uncharged; the total number of these particles in the nucleus is known as the *mass number* (A).

The number of protons in the nucleus is known as the *atomic number* (Z). All the atoms of a particular chemical element have the same atomic number, but while the number of protons is constant, the number of neutrons (N) in the atoms, and thus their masses (mass numbers), may vary. These different forms of the same element are known as *isotopes* of the element and these isotopes differ in some of their physical properties.

Each electron carries a negative charge which is of the same magnitude as the positive charge of the proton, so that in the neutral atom the number of electrons is equal to the number of protons in the nucleus.

Some isotopes may be stable, the differences between them arising solely from their difference in mass; others may be radioactive (*radioisotopes*), their unstable nuclei changing spontaneously and emitting particles or electromagnetic waves, or both, in an attempt to move towards a more stable nuclear arrangement (see also Radioactive Decay, below).

Most of the naturally occurring isotopes are stable, though there are some that are unstable and therefore radioactive, for example, uranium-235. In addition, artificial radionuclides are prepared by converting stable nuclei into unstable forms or naturally occurring radionuclides may be prepared by artificial means.

Nomenclature. The symbol used for a nuclide is a development of the chemical symbol for the atom, with the mass number (A) as a left or preceding superscript and the atomic number (Z) as a left subscript; the neutron number (N) has occasionally been given as a right subscript. Thus, element X may be depicted as: ${}^{A}_{Z}X_{N}$. However, the neutron number may be inferred so it is almost always omitted. Thus the symbols for the 3 hydrogen isotopes—common hydrogen, deuterium, and tritium—would be ${}^{1}_{1}H$, ${}^{2}_{1}H$, and ${}^{3}_{1}H$, and the symbols for the 3 naturally occurring uranium isotopes ${}^{234}_{92}U$, ${}^{235}_{92}U$, and ${}^{238}_{92}U$. As the atomic number can also be inferred from the chemical symbol it is usual to omit the subscript and refer to, for example, ^{3}H or ^{235}U. It is also common practice to write out the full name of the element followed by the mass number, e.g. chromium-51 for ^{51}Cr.

Radioactive Decay

Radionuclides decay (transform to more stable nuclides) in various ways that depend upon their initial structure. Each radionuclide has a distinct half-life, which is the time taken for a given quantity to decay to one half of its initial value or original activity. The activity of radionuclides is measured in terms of the rate of transformation or disintegration. The SI unit for radioactivity is the becquerel (Bq), which equals 1 disintegration/second (or 1 transformation/second). The SI units are metric and technically are the preferred method of quantifying radioactivity. However, the older system using curies (Ci) may still be used in practice; $1\ Ci = 3.7 \times 10^{10}\ Bq$.

Radioactive decay or transformation may involve the emission of charged particles, electron capture, or isomeric transition. The type of emission from a radionuclide largely determines its usefulness in medicine. The products of decay may themselves be radioactive and undergo further transformation, e.g. the decay of molybdenum-99 to technetium-99m, which undergoes further decay to technetium-99. Most sources emit more than one type of radiation.

Alpha decay emits alpha particles from the nucleus; these are positively charged particles (identical to a helium nucleus) consisting of 2 protons and 2 neutrons. Alpha decay occurs in elements with high atomic mass. These radionuclides are rarely used in nuclear medicine because elements of high atomic mass are uncommon in biological systems such as the human body. In addition, alpha particles have limited penetrative power, but the dense ionisation they produce results in high tissue damage. They are also difficult to detect so are of little use in imaging.

Beta decay emits beta particles from the nucleus at high velocity; each particle carries a charge and has a mass equal to that of an electron. A negatively charged beta particle (or negatron) (β^-) is therefore identical to an electron. Negative beta decay occurs in atoms with an excess of neutrons and results in the conversion of neutrons to protons. A positively charged beta particle is also called a positron (β^+). *Positron decay* usually occurs in atoms with an excess of protons, and these are effectively converted into neutrons. A positron has only a transient existence and after losing its energy, it interacts with an electron and is annihilated, producing gamma rays (see below) in the process. Radiopharmaceuticals that contain β^--emitting radionuclides such as iodine-131 (^{131}I) are common in radiotherapy, whereas positron-emitters such as carbon-11 (^{11}C), fluorine-18 (^{18}F), nitrogen-13 (^{13}N), and oxygen-15 (^{15}O) are used mainly in positron emission tomography (PET) imaging. Single photon emission computed tomography (SPECT) is a similar technique to PET, using gamma-ray emitting radionuclides.

Gamma radiation is electromagnetic radiation that occurs when the nucleus eliminates excess energy by means of *photon* emission. Photons are uncharged and highly penetrative.

In the process of *electron capture* (EC; or K-capture), an electron from an inner shell is drawn into the nucleus, and electromagnetic radiation in the form of *X-rays* is produced. (The distinction between X-rays and gamma radiation is now considered to be that the latter arises from the nucleus while the former are produced by electron events.)

The decay from an excited nuclear state to a lower energy state is called *isomeric transition* (IT), which can accompany beta- or positron-decay or EC, and may emit gamma rays. If the excited state occurs for long enough to be measurable, it is called a metastable state and denoted by the suffix m attached to the mass number e.g. technetium-99m or ^{99m}Tc. Another form of IT occurs when a gamma photon from the nucleus strikes an orbital electron, dislodging the electron; this is termed *internal conversion*, and X-rays are emitted. If the originally displaced electron energy is transferred to another electron, an *Auger electron* is produced. X-rays produced from internal conversion or electron capture are of little use in nuclear medicine.

Supply, Preparation, and Control

Radiopharmaceuticals can be classified by half-life into those with long half-lives (over 12 hours), which can be manufactured commercially and supplied to the user as a finished product, and those with short half-lives (less than 12 hours) which need to be prepared in hospital radiopharmacies as commercial supply is impractical. Most countries have regulations concerning the preparation, use, transport, storage, and disposal of such compounds.

Radionuclides may be produced in nuclear reactors, particle accelerators, or generators. Medically useful isotopes produced in a nuclear reactor include molybdenum-99 (^{99}Mo), iodine-131 (^{131}I), phosphorus-32 (^{32}P), and xenon-133 (^{133}Xe). Many radionuclides used in nuclear medicine are produced in an accelerator such as a cyclotron; these include iodine-123 (^{123}I), indium-111 (^{111}In), gallium-67 (^{67}Ga), and thallium-201 (^{201}Tl). Generators are systems that contain both a parent and daughter radionuclide in equilibrium; ideally the parent radioisotope will have a significantly longer half-life than the daughter radioisotope. However, the daughter half-life should be sufficiently long enough for it to be obtained from the generator, prepared in the desired dose, and delivered to the patient, but still short enough to minimise radiation exposure to the patient by decaying to a non-radioactive component in a timely fashion. Generator-produced radionuclides include technetium-99m (^{99m}Tc), gallium-68 (^{68}Ga), and krypton-81m (^{81m}Kr).

Radiopharmaceutical kits allow pharmacists to radiolabel a desired ligand (the properties of which are mainly responsible for dictating how the product will behave in the body); most pharmaceutical kits use technetium-99m (^{99m}Tc) as the radioisotope.

Most radiopharmaceuticals require storage in an airtight container that is sufficiently shielded to protect from primary and secondary emissions, and that complies with national and international regulations. During storage, containers may darken due to irradiation, although this does not necessarily involve deterioration of the preparations.

General Uses

Radiopharmaceuticals are used in the diagnosis of many clinical conditions and as a source of radiation for the treatment of disease. These include:

- static imaging procedures to provide structural or functional information; some radiopharmaceuticals concentrate in the normal tissue, and the diseased tissue appears as an area of reduced activity (a 'cold' area), whereas others concentrate in diseased tissue which appears as an area of increased activity (a 'hot' area)
- dynamic imaging procedures which provide functional information about an organ, showing how the radiopharmaceutical is handled by the organ over a period of time
- uptake and retention measurements using counting equipment to measure the ability of an organ or the body to concentrate and retain a radiopharmaceutical
- clearance measurements which measure the rate at which a radiopharmaceutical clears from the blood
- dilution techniques in which the total volume of a body fluid is determined by measuring the dilution of a radiopharmaceutical
- therapeutic procedures in which the radiation emitted by the radiopharmaceutical is used to destroy diseased tissue

Specific procedures include the following:

- bone scans to detect and stage bone disease, or assess bone viability
- cardiology: myocardial perfusion; myocardial viability; cardiac blood pool studies (to assess cardiac function such as left ventricular ejection fraction)
- CNS: CSF physiological imaging; blood flow assessment; brain metabolism
- endocrine procedures: thyroid, parathyroid, and adrenal scans; thyroid uptake assessment
- gastrointestinal procedures: gastrointestinal motility; gastrointestinal bleeding localisation
- liver and spleen imaging
- genito-urinary imaging including renal function assessment
- infection imaging using gallium scans or leucocyte scans
- lymphatic procedures to assess lymphatic flow using sentinel node imaging or lymphangiography
- non-imaging procedures: *Helicobacter pylori* breath test; red cell mass; plasma volume
- in oncology to localise and assess suspected and proven cancers: somatostatin receptor imaging; prostate cancer imaging; scintimammography; glucose metabolism imaging
- radionuclide therapy: thyroid ablation; bone pain palliation; polycythaemia vera treatment; non-Hodgkin's lymphoma treatment
- respiratory function: ventilation and perfusion lung imaging for the detection of pulmonary emboli

Adverse Effects and Precautions

Ionising radiation can be delivered using external sources (such as external beam radiation therapy) or internally via radioactive implants, seeds, wires, or plaques placed within or near the target tumour, (brachytherapy) or via the use of systemic radioisotopes. Radiation therapy damages DNA, and is most effective against rapidly dividing cells. Hypoxic, poorly vascularised tissues are less sensitive to the effects of radiation, and some large bulky tumours are relatively radioresistant because of tumour hypoxia.

All cross-references refer to entries in Volume A

Adverse effects of radiation may be acute or delayed, and depend on the organ most affected. Rapidly proliferating tissues such as the skin, mucosa, and bone marrow often suffer acute effects such as desquamation, erythema, and cytopenias. Long term sequelae are tissue specific and usually occur if normal tissue tolerance is exceeded; careful dosimetry and radiation planning are important to ensure treatment does not exceed a maximum tolerated dose. Secondary tumours can occur.

Penetration potential of radionuclides is also a factor. Alpha particles have only a short range and skin is thick enough to protect from alpha radiation. However, if ingested, extensive damage can occur. Exposure is not usually an issue since alpha-emitters are rarely used in nuclear pharmacy. However, since monitoring is difficult, insidious exposure can occur. Ingestion of beta-emitting isotopes, especially radioisotopes of carbon, hydrogen, sulfur, and phosphorus, can have severe consequences, as these can be deposited into tissues causing extensive damage; their prolonged half-lives also mean they can cause genetic problems. However, since beta emission is easily monitored, workers can be aware of shielding needs. Gamma photons penetrate skin and tissue easily, although of the typical emissions used in nuclear pharmacy, it is least worrisome in terms of tissue damage.

Many of the adverse effects of radiopharmaceuticals have been attributed to carriers or contaminants. Reported adverse reactions include rash, gastrointestinal disturbances, headache, light-headedness, chest discomfort, and hypersensitivity reactions including anaphylaxis.

Many radiopharmaceuticals are excreted in breast milk, and temporary cessation of breast feeding is recommended for some, such as iodine-131 (^{131}I) and technetium-99m (^{99m}Tc).

References.
1. Silberstein EB, Ryan J. Pharmacopeia Committee of the Society of Nuclear Medicine. Prevalence of adverse reactions in nuclear medicine. *J Nucl Med* 1996; 37: 185–92.
2. Silberstein EB. Pharmacopeia Committee of the Society of Nuclear Medicine. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. *J Nucl Med* 1998; 39: 2190–2.
3. Stabin MG, Breitz HB. Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. *J Nucl Med* 2000; 41: 863–73.
4. Mazzarri W, *et al.* The radiation burden of radiological investigations. *Arch Dis Child* 2007; 92: 1127–31.
5. Santos-Oliveira R. Undesirable events with radiopharmaceuticals. *Tohoku J Exp Med* 2009; 217: 251–7.

Carbon-11

Carbone-11; Carbonio-11; Carbono 11; Carbono-11; Hiili-11; Karbon-11; Kohlenstoff-11; Kol-11; Koolstof-11; Szén-11; Węgiel-11; Углерод-11.

CAS — 14333-33-6 (carbon-11); 10456-04-9 (carbon monoxide (^{11}C)); 94153-50-1 (mespiperone (^{11}C)); 58576-49-1 (methionine (^{11}C)); 97849-54-2 (raclopride (^{11}C)).

UNII — 07BH0IKF2I (carbon monoxide (^{11}C)); GE077RPG04 (raclopride (^{11}C)); Y1WPQ66L9G (sodium acetate (^{11}C)).

NOTE. Carbon Monoxide C 11 is *USAN*.
Mespiperone (^{11}C) is *rINN* and Mespiperone C 11 is *USAN*.
Raclopride C 11 is *USAN*.
HALF-LIFE. 20.4 minutes.

Profile

Carbon-11 (^{11}C) is a radioactive isotope of carbon that emits positrons and gamma rays. It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1). In theory almost any organic molecule can be labelled with carbon-11, although its short half-life may limit the useful yield in prolonged syntheses. Labelled compounds for which official standards exist include L-methionine for the detection of malignant neoplasms, acetate for the study of myocardial metabolism and imaging of malignant neoplasms, raclopride and mespiperone for the study of CNS dopaminergic D_2 and D_3 receptors, and flumazenil for the study of GABA receptors. Labelled carbon monoxide has been used to assess blood volume.

Other substances that have been labelled with carbon-11 include *meta*-hydroxyephedrine and beta blockers to study sympathetic innervation, carfentanil and diprenorphine to image opiate receptors, and palmitate for myocardial metabolic studies. Pittsburgh Compound B (PIB; N-methyl-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole) labelled with carbon-11 has been investigated for the imaging of beta amyloid and possible diagnosis of Alzheimer's disease.

References.
1. Klein LJ, *et al.* Carbon-11 acetate as a tracer of myocardial oxygen consumption. *Eur J Nucl Med* 2001; 28: 651–68.
2. Halldin C, *et al.* PET studies with carbon-11 radioligands in neuropsychopharmacological drug development. *Curr Pharm Des* 2001; 7: 1907–29.
3. Dence CS, *et al.* Imaging myocardium enzymatic pathways with carbon-11 radiotracers. *Methods Enzymol* 2004; 389: 286–315.
4. Song WS, *et al.* Normal organ standard uptake values in carbon-11 acetate PET imaging. *Nucl Med Commun* 2009; 30: 462–5.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: L-Methionine ((^{11}C)Methyl) Injection; Flumazenil (N-(^{11}C)Methyl) Injection; Raclopride ((^{11}C)Methoxy) Injection; Sodium Acetate ((1-^{11}C)) Injection;
USP 36: Carbon Monoxide C 11; Flumazenil C 11 Injection; Mespiperone C 11 Injection; Methionine C 11 Injection; Raclopride C 11 Injection; Sodium Acetate C 11 Injection.

Carbon-14

Carbone-14; Carbonio-14; Carbono 14; Carbono-14; Hiili-14; Karbon-14; Kohlenstoff-14; Kol-14; Koolstof-14; Szén-14; Węgiel-14; Углерод-14.

CAS — 14762-75-5.

UNII — 7V681S677O (carbon-14); WBZ6M63TEE (urea (^{14}C)).

HALF-LIFE. 5730 years.

Profile

Carbon-14 (^{14}C) is a radioactive isotope of carbon; it is a pure beta particle emitter (see Radioactive Decay, p. 2222.1). It has been used to label various organic compounds; these are then used in breath tests.

Urea (p. 1727.3) labelled with carbon-14 is used in a breath test to detect *Helicobacter pylori* as an aid in the diagnosis of peptic ulcer disease (p. 1813.2).

Carbon-13 (^{13}C) (see p. 2470.3) is a stable (non-radioactive) isotope of carbon that is used similarly.

References.
1. Warwick T. Carbon-14-urea breath test: a cautionary note. *J Nucl Med* 1996; 37: 1916.
2. Balon H, *et al.* Society of Nuclear Medicine. Procedure guideline for carbon-14-urea breath test. *J Nucl Med* 1998; 39: 2012–14.
3. Leide-Svegborn S, *et al.* Biokinetics and radiation doses for carbon-14 urea in adults and children undergoing the Helicobacter pylori breath test. *Eur J Nucl Med* 1999; 26: 573–80.
4. Abrams DN, *et al.* Pharmaceutical interference with the ^{14}C carbon urea breath test for the detection of Helicobacter pylori infection. *J Pharm Pharm Sci* 2000; 3: 228–33.
5. McCarthy KE. Recent advances in the design and synthesis of carbon-14 labelled pharmaceuticals from small molecule precursors. *Curr Pharm Des* 2000; 6: 1057–83.
6. Higazy E, *et al.* The impact of brushing teeth on carbon-14 urea breath test results. *J Nucl Med Technol* 2000; 28: 162–4.
7. Öztürk E, *et al.* A new, practical, low-dose ^{14}C-urea breath test for the diagnosis of Helicobacter pylori infection: clinical validation and comparison with the standard method. *Eur J Nucl Med Mol Imaging* 2003; 30: 1457–62.
8. Özdemir E, *et al.* Could the simplified ^{14}C urea breath test be a new standard in noninvasive diagnosis of Helicobacter pylori infection? *Ann Nucl Med* 2008; 22: 611–16.
9. Bentur Y, *et al.* Safety of ^{14}C-UBT for diagnosis of Helicobacter pylori infection in pregnancy. *Can Fam Physician* 2009; 55: 479–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: HeliCap†; *Neth.*: HeliCap; *Port.*: HeliCap; *Swed.*: Heliprobe; *USA*: Pytest.

Pharmacopoeial Preparations
USP 36: Urea C 14 Capsules.

Chromium-51

Chrom-51; Chrome-51; Chroom-51; Cromo 51; Króm-51; Krom-51; Kromi-51; Хром-51.

CAS — 14392-02-0 (chromium-51); 16284-59-6 (chromic chloride (^{51}Cr)); 27849-89-4 (chromium edetate (^{51}Cr)); 7775-11-3 (sodium chromate (^{51}Cr)).

ATC — V09CX04 (chromium edetate (51Cr)).

ATC Vet — QV09CX04 (chromium edetate (51Cr)); QV09GX03 (chromate labelled cells (51Cr)).

UNII — 9QAU17N705 (chromium-51); N3Y22O955Z (chromium edetate (^{51}Cr)).

NOTE. Chromic Chloride Cr 51 is *USAN*.
Chromic Phosphate Cr 51 is *USAN*.
Sodium Chromate (^{51}Cr) is *rINN* and Sodium Chromate Cr 51 is *USAN*.
HALF-LIFE. 27.7 days.

Profile

Chromium-51 (^{51}Cr) is a radioactive isotope of chromium (p. 2055.3) that emits X-rays, gamma rays, and Auger electrons (see Radioactive Decay, p. 2222.1). As sodium chromate (^{51}Cr), it is used to label red blood cells so that red cell survival and red cell volume can be measured. Chromium-51 activity in the faeces can be used to estimate gastrointestinal blood losses. Red blood cells labelled with chromium-51 and damaged by heat before re-injection have been used for spleen scanning.

As chromium edetate (^{51}Cr), chromium-51 has been used in the determination of the GFR.

As chromic chloride (^{51}Cr), chromium-51 has been given for the determination of loss of serum protein into the gastrointestinal tract. It has also been used to label albumin for the determination of protein-losing enteropathy.

References.
1. Godfrey T, *et al.* Chromium-51 ethylenediamine tetraacetic acid glomerular filtration rate: a better predictor than glomerular filtration rate calculated by the Cockcroft-Gault formula for renal involvement in systemic lupus erythematosus patients. *Rheumatology (Oxford)* 2001; 40: 324–8.
2. Bird NJ, *et al.* Extracellular distribution volumes of hydrophilic solutes used to measure the glomerular filtration rate: comparison between chromium-51-EDTA and iohexol. *Physiol Meas* 2007; 28: 223–34.
3. Dworkin HJ, *et al.* Comparison of red cell and whole blood volume as performed using both chromium-51-tagged red cells and iodine-125-tagged albumin and using I-131-tagged albumin and extrapolated red cell volume. *Am J Med Sci* 2007; 334: 37–40.
4. Bird NJ, *et al.* Reproducibilities and responses to food intake of GFR measured with chromium-51-EDTA and iohexol simultaneously and independently in normal subjects. *Nephrol Dial Transplant* 2008; 23: 1902–9.
5. Kumar P, *et al.* Estimation of blood volume in burns patients using *radioisotope chromium-51: a pilot study. Burns* 2007; 33: 1072–3.
6. Descazeaud A, *et al.* Committee for Lower Urinary Tract Symptoms of the French Association of Urology. Blood loss during transurethral resection of the prostate as measured by the chromium-51 method. *J Endourol* 2010; 24: 1813–16.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Chromium(^{51}Cr) Edetate Injection; Sodium Chromate (^{51}Cr) Sterile Solution;
USP 36: Chromium Cr 51 Edetate Injection; Sodium Chromate Cr 51 Injection.

Cobalt-57

Cobalto 57; Kobalt-57; Kobolt-57; Koboltti-57; Кобальт-57.

CAS — 13981-50-5 (cobalt(57)); 16413-89-9 (cobaltous (^{57}Co) chloride); 13115-03-2 (cyanocobalamin (^{57}Co)); 41559-38-0 (cyanocobalamin (^{57}Co)).

ATC — V09XX01 (cobalt cyanocobalamin (57Co)).

ATC Vet — QV09XX01 (cobalt cyanocobalamin (57Co)).

UNII — 72GWV0852V (cobalt-57); ZL40NE830Q (cobaltous (^{57}Co) chloride); 025P9I542Y (cyanocobalamin (^{57}Co)).

NOTE. Cobaltous Chloride Co 57 is *USAN*.
Cyanocobalamin (^{57}Co) is *rINN* and Cyanocobalamin Co 57 is *USAN*.
HALF-LIFE. 271.8 days.

Profile

Cobalt-57 (^{57}Co) is a radioactive isotope of cobalt (p. 2482.2) that emits X-rays and gamma rays and decays by electron capture (see Radioactive Decay, p. 2222.1). An aqueous solution or capsules of cyanocobalamin (^{57}Co) have been given orally in the Schilling test for the measurement of absorption of vitamin B_{12} in the diagnosis of pernicious anaemia and other malabsorption syndromes (see under Vitamin B_{12} Substances, p. 2108.1). It is also used with cyanocobalamin (^{58}Co), see below.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Dicopac†.

Pharmacopoeial Preparations
Ph. Eur.: Cyanocobalamin(^{57}Co) Capsules; Cyanocobalamin (^{57}Co) Solution;
USP 36: Cyanocobalamin Co 57 Capsules; Cyanocobalamin Co 57 Oral Solution.

Cobalt-58

Cobalto 58; Kobalt-58; Kobolt-58; Koboltti-58; Кобальт-58.

CAS — 13981-38-9 (cobalt-58); 18195-32-9 (cyanocobalamin (^{58}Co)).

ATC — V09XX02 (cobalt cyanocobalamin (58Co)).

ATC Vet — QV09XX02 (cobalt cyanocobalamin (58Co)).

UNII — U0E93N6V2A (cyanocobalamin (^{58}Co)).

HALF-LIFE. 70.9 days.

Profile

Cobalt-58 (^{58}Co) is a radioactive isotope of cobalt (p. 2482.2) that emits Auger electrons, X-rays, gamma rays, and decays by positron emission (see Radioactive Decay, p. 2222.1). An aqueous solution or capsules of cyanocobalamin (^{58}Co) have been given orally in the Schilling test for the measurement of absorption of vitamin B_{12} in the diagnosis of pernicious anaemia and other malabsorption syndromes (see under Vitamin B_{12} Substances, p. 2108.1).

The different emissions of cobalt-57 and cobalt-58 allow the isotopes to be distinguished. This can be used to differentiate between failure of absorption due to lack of intrinsic factor (pernicious anaemia) and that due to ileal malabsorption, by giving both free cyanocobalamin (^{58}Co)

and cyanocobalamin (^{57}Co) bound to intrinsic factor. A dual isotope kit has been used for this purpose.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Dicopac†.

Pharmacopoeial Preparations
Ph. Eur.: Cyanocobalamin(^{58}Co) Capsules; Cyanocobalamin (^{58}Co) Solution;
USP 36: Cyanocobalamin Co 58 Capsules.

Erbium-169

Erb-169; Erbio 169; Érbio-169; Эрбий-169.
CAS — 15840-13-8.
ATC — V10AX04 (erbium citrate colloid (^{169}Er)).
ATC Vet — QV10AX04 (erbium citrate colloid (^{169}Er)).

HALF-LIFE. 9.4 days.

Profile

Erbium-169 (^{169}Er) is a radioactive isotope of erbium. A colloidal suspension of erbium citrate (^{169}Er), is used by local injection for the treatment of arthritic conditions particularly of the small joints after failure of intra-articular corticosteroid therapy or when corticosteroids are contra-indicated.

References.

1. Manil L, *et al.* Physical and biological dosimetry in patients undergoing radiosynoviorthesis with erbium-169 and rhenium-186. *Nucl Med Commun* 2001; 22: 405–16.
2. van der Zant FM, *et al.* Radiation synovectomy with ^{90}yttrium, ^{186}rhenium and ^{169}erbium: a systematic literature review with meta-analyses. *Clin Exp Rheumatol* 2009; 27: 130–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Ermm-1.

Fluorine-18

Flúor 18; Fluor-18; Fluori-18; Fluoro-18; Фтор-18.
CAS — 13981-56-1 (fluorine-18); 902143-01-5 (florbetaben (^{18}F)); 956103-76-7 (florbetapir (^{18}F)); 879894-01-6 (fluciclatide (^{18}F)); 222727-39-1 (fluciclovine (^{18}F)); 105851-17-0 (fludeoxyglucose (^{18}F)); 92812-82-3 (fluorodopa (^{18}F)); 863887-89-2 (flurpiridaz (^{18}F)); 765922-62-1 (flutemetamol (^{18}F)); 22554-99-0 (sodium fluoride (^{18}F)).
ATC — V09AX05 (florbetapir ($_{18}$F)); V09IX04 (fludeoxyglucose ($_{18}$F)); V09IX05 (fluorodopa ($_{18}$F)); V09IX06 (sodium fluoride ($_{18}$F)).
ATC Vet — QV09AX05 (florbetapir ($_{18}$F)); QV09IX04 (fludeoxyglucose ($_{18}$F)) QV09IX05 (fluorodopa ($_{18}$F)); QV09IX06 (sodium fluoride ($_{18}$F)).
UNII — 0Z5B2CJX4D (fludeoxyglucose (^{18}F)); 2C59820SQX (fluorodopa (^{18}F)); TLA7312TOI (florbetaben (^{18}F)); 6W15Z5R0RU (florbetapir (^{18}F)); 9L75099X6R (sodium fluoride (^{18}F)).

NOTE. Florbetaben (^{18}F) is *rINN*.
Florbetapir (^{18}F) is *rINN* and Florbetapir F 18 is *USAN*.
Fluciclatide (^{18}F) is *rINN* and Fluciclatide F 18 is *USAN*.
Fluciclovine (^{18}F) is *rINN*.
Fludeoxyglucose (^{18}F) is *rINN* and Fludeoxyglucose F 18 is *USAN*.
Fluorodopa (^{18}F) is *rINN* and Fluorodopa F 18 is *USAN*.
Flurpiridaz (^{18}F) is *rINN* and Flurpiridaz F 18 is *USAN*.
Flutemetamol (^{18}F) is *rINN*.
HALF-LIFE. 110 minutes.

Profile

Fluorine-18 (^{18}F) is a radioactive isotope of fluorine that emits positrons. It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1).

Various substances have been labelled with fluorine-18 for diagnostic purposes; among those for which official standards exist, fludeoxyglucose (^{18}F) (2-deoxy-2-fluoro-^{18}F-α-D-glucopyranose; ^{18}F-fluorodeoxyglucose; ^{18}F-FDG) is given by intravenous injection for the assessment of cerebral and myocardial glucose metabolism in various physiological or pathological states. It is also used for the evaluation and detection of malignant tumours including those of the brain, head and neck, lung, colon and rectum, and thyroid gland, as well as for lymphoma and malignant melanoma. It has also been occasionally used for renal imaging. Florbetapir (^{18}F) (4-[(1*E*)-2-(6-[2-[2-(2-[^{18}F]Fluoroethoxy)ethoxy]ethoxy)pyridin-3-yl)ethenyl]-*N*-methylbenzenamine; 18F-AV-45) is given intravenously for the imaging of beta-amyloid neuritic plaque density in the brain of patients being evaluated for Alzheimer's disease and other causes of cognitive impairment. Fluorodopa (^{18}F) (^{18}F-FD) is also used in cerebral imaging and assessment of dopaminergic neurons. Sodium fluoride (^{18}F) is used in bone scanning.

Other carrier substances that have been labelled with fluorine-18 for imaging procedures include choline (Fluorocholine (^{18}F) or Fluoroethylcholine (^{18}F)), thymidine (^{18}F-FLT), opiate receptor antagonists, and beta blockers. Florbetaben (^{18}F) (Bay-94-9172) is also being investigated for imaging of beta-amyloid plaques in the study of Alzheimer's disease. Fluciclatide (^{18}F) ([^{18}F]AH-111585) is being studied as an imaging agent in the evaluation of anti-angiogenic therapy.

References.

1. Giorgetti A, *et al.* Clinical oncological applications of positron emission tomography (PET) using fluorine-18-fluoro-2-deoxy-D-glucose. *Radiol Med* 2002; 103: 293–318.
2. Liu S-H, *et al.* False positive fluorine-18 fluorodeoxy-D-glucose positron emission tomography finding caused by osteoradionecrosis in a nasopharyngeal carcinoma patient. *Br J Radiol* 2004; 77: 257–60.
3. Dollé F. Fluorine-18-labelled fluoropyridines: advances in radiopharmaceutical design. *Curr Pharm Des* 2005; 11: 3221–35.
4. Khan N, *et al.* Review of fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in the follow-up of medullary and anaplastic thyroid carcinomas. *Cancer Control* 2005; 12: 254–60.
5. Wester HJ, Schottelius M. Fluorine-18 labeling of peptides and proteins. *Ernst Schering Res Found Workshop* 2007: 79–111.
6. Kwee SA, *et al.* Cancer imaging with fluorine-18-labeled choline derivatives. *Semin Nucl Med* 2007; 37: 420–8.
7. de Beco V, *et al.* Le fluor 18 en radiopharmacie. *Ann Pharm Fr* 2008; 66: 60–5.
8. Terasawa T, *et al.* Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review. *J Clin Oncol* 2009; 27: 1906–14.
9. Kasper B, *et al.* The use of fluorine-18 fluorodesoxyglycose-positron emission tomography for treatment monitoring in patients with soft tissue sarcomas. *Heil J Nucl Med* 2010; 13: 40–4.
10. Clark CM, *et al.* AV45-A07 Study Group. Use of florbetapir-PET for imaging β-amyloid pathology. *JAMA* 2011; 305: 275–83. Correction. *ibid.*; 1096.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: 18F-FDG; *Belg.*: Glucotrace; *China*: Fu Tang Pai Te (氟唐派特); Cz.: Efdege; FDG Scan†; GlucoRos; *Denm.*: PCA (18F); *Fin.*: Steripet; *Fr.*: Cisnaf; Dopacis; Flucis; Glucotep; Gluscan; *Hung.*: Pozitron-Scan-FDG; *Irl.*: Dopacis; Ertracer; *Ital.*: Efdege; Glucompet; Steripet†; *Neth.*: Dopacis; Efdege; FDG Scan F18†; Flucis; Glucotrace; SteriPet; *Port.*: Contracer; Efdege; Flucis; Steripet; *Spain*: Barnascan; Dopacis; Farna FDG; FDG Scan†; FDGCadpet; Flucis; Fluodos; Fluorscan; Fluotracer; Metabolimax; MetaTrace; Steripet†; *UK*: Amyvid; *USA*: Amyvid; Vizamyl.

Multi-ingredient Preparations. *Spain*: Gluscan.

Pharmacopoeial Preparations
Ph. Eur.: Fludeoxyglucose (^{18}F) Injection; Fluoride (^{18}F) Solution for Radiolabelling; Sodium Fluoride (^{18}F) Injection;
USP 36: Fludeoxyglucose F 18 Injection; Fluorodopa F 18 Injection; Sodium Fluoride F 18 Injection.

Gallium-67

Gal 67; Galio 67; Gàlio-67; Gallio-67; Галлий-67.
CAS — 14119-09-6 (gallium-67); 41183-64-6 (gallium citrate (^{67}Ga)); 52260-70-5 (gallium citrate (^{67}Ga)).
ATC — V09HX01 (gallium citrate ($_{67}$Ga)).
ATC Vet — QV09HX01 (gallium citrate ($_{67}$Ga)).
UNII — 99T03J52W0 (gallium-67); 4LJK511Z86 (gallium citrate (^{67}Ga)).

NOTE. Gallium (^{67}Ga) Citrate is *rINN* and Gallium Citrate Ga 67 is *USAN*.
HALF-LIFE. 3.26 days.

Profile

Gallium-67 (^{67}Ga) is a radioactive isotope of gallium that decays by electron capture with emission of X-rays (see Radioactive Decay, p. 2222.1). It is used in the form of an intravenous injection of gallium citrate (^{67}Ga).

Gallium in the form of gallium citrate (^{67}Ga) is taken up by iron-binding proteins (transferrin and lactoferrin) and is thus concentrated in some malignant tumours of the lymphatic system, as well as in some other tissues, and may be used for tumour visualisation. It may also be used to determine the response to chemotherapy and detect recurrence of suitable tumours. Concentration of lactoferrin also occurs in inflammatory lesions and gallium-67 is therefore used for the localisation of focal inflammatory sites, such as may occur in abscesses, or sarcoidosis. Gallium scans have proved useful for the detection of various infections such as pneumonia encountered in patients with AIDS.

References.

1. Kostakoglu L, Goldsmith SJ. Positron emission tomography in lymphoma: comparison with computed tomography and Gallium-67 single photon emission computed tomography. *Clin Lymphoma* 2000; 1: 67–74.
2. Even-Sapir E, Israel O. Gallium-67 scintigraphy: a cornerstone in functional imaging of lymphoma. *Eur J Nucl Med Mol Imaging* 2003; 30 (suppl 1): S65–S81.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to gallium-67 since radioactivity has been reported to be present in breast milk for 2 weeks.

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 01/07/04)

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Gallium(^{67}Ga) Citrate Injection;
USP 36: Gallium Citrate Ga 67 Injection.

Gallium-68

Gal 68; Gàlio-68; Gallio-68.
CAS — 15757-14-9.

HALF-LIFE. 67.6 minutes.

Profile

Gallium-68 (^{68}Ga) is a radioactive isotope of gallium that emits positrons, Auger electrons, X-rays and gamma rays (see Radioactive Decay, p. 2222.1). It is used in positron-emission tomography to radiolabel a somatostatin analogue in order to image neuroendocrine and other tumours.

References.

1. Win Z, *et al.* Somatostatin receptor PET imaging with gallium-68 labeled peptides. *Q J Nucl Med Mol Imaging* 2007; 51: 244–50.
2. Al-Nahhas A, *et al.* Gallium-68 PET: a new frontier in receptor cancer imaging. *Anticancer Res* 2007; 27: 4087–94.
3. Khan MU, *et al.* Clinical indications for gallium-68 positron emission tomography imaging. *Eur J Surg Oncol* 2009; 35: 561–7.
4. Pagou M, *et al.* Can gallium-68 compounds partly replace ^{18}F-FDG in PET molecular imaging? *Hell J Nucl Med* 2009; 12: 102–5.

Indium-111

Ind-111; Indio 111; Índio-111; Индий-111.
CAS — 15750-15-9 (indium-111); 139039-70-6 (indium (^{111}In) altumomab pentetate); 10025-82-8 (indium (^{111}In) chloride); 65389-08-4 (indium (^{111}In) hydroxyquinoline); 139096-04-1 (indium (^{111}In) pentetreotide); 138955-27-8 (indium (^{111}In) satumomab pendetide).
ATC — V09AX01 (indium pentetate (mIn)); V09GX02 (indium imciromab (mIn)); V09HB01 (indium oxinate labelled cells (mIn)); V09HB02 (indium tropolonate labelled cells (mIn)); V09IB01 (indium pentetreotide (mIn)); V09IB02 (indium satumomab pendetide (mIn)); V09IB03 (indium antiovarium-carcinoma antibody (mIn)); V09IB04 (indium capromab pendetide (mIn)).
ATC Vet — QV09AX01 (indium pentetate (mIn)); QV09GX02 (indium imciromab (mIn)); QV09HB01 (indium oxinate labelled cells (mIn)); QV09HB02 (indium tropolonate labelled cells (mIn)); QV09IB01 (indium pentetreotide (mIn)); QV09IB02 (indium satumomab pendetide (mIn)); QV09IB03 (indium antiovariumcarcinoma antibody (mIn)); QV09IB04 (indium capromab pendetide (mIn)).
UNII — E9NGC49E0T (indium-111); WJZ06C0H8L (indium-111 ion); 58TD96H03I (indium (^{111}In) chloride); S9U4ZR2W8V (indium (^{111}In) ibritumomab tiuxetan); LGX9OL562T (indium (^{111}In) oxyquinoline); 5K3UP561AX (indium (^{111}In) pentetate); 7UIT3ZGC8E (indium (^{111}In) pentetate disodium); M3121J6Z32 (indium (^{111}In) pentetreotide).

NOTE. Indium In 111 Altumomab Pentetate, Indium In 111 Oxyquinoline, and Indium In 111 Pentetreotide are *USAN*. Indium[^{111}In] Satumomab Pendetide is *BAN* and Indium In 111 Satumomab Pendetide is *USAN*.
HALF-LIFE. 67 hours (2.8 days).

Profile

Indium-111 (^{111}In) is a radioactive isotope of indium that decays by electron capture with emission of X-rays (see Radioactive Decay, p. 2222.1). It is complexed with pentetic acid (pentetate) and used intrathecally in diagnostic CSF studies.

Leucocytes labelled with indium (^{111}In) hydroxyquinoline (indium (^{111}In) oxyquinoline or indium (^{111}In) oxine) are used for the location of inflammatory lesions; applications have been the detection or localisation of abscesses or infections and the evaluation of inflammatory bowel disease. Platelets have been similarly labelled.

Indium (^{111}In) bleomycin has been given by intravenous injection for the detection of tumours. Indium (^{111}In) pentetreotide is used for the detection and localisation of tumours originating from neuroendocrine cells.

Monoclonal antibodies such as capromab pendetide and ibritumomab tiuxetan have been labelled with indium-111 in the form of indium (^{111}In) chloride. These are used for the

detection and imaging of malignant neoplasms. Other monoclonal antibodies that have been labelled with indium-111 include altumomab pentetate, imciromab pentetate, and satumomab pendetide. Uses include the detection, diagnosis, and evaluation of malignant neoplasms as well as the detection and localisation of myocardial infarction.

References.
1. Medina M, *et al.* Indium-111 labelled white blood cell scintigraphy in cranial and spinal septic lesions. *Eur J Nucl Med* 2000; 27: 1473–80.
2. Nathan J, *et al.* Fused SPECT/CT imaging of peri-iliopsoas infection using indium-111-labeled leukocytes. *Clin Nucl Med* 2006; 31: 801–2.
3. Manyak MJ. Indium-111 capromab pendetide in the management of recurrent prostate cancer. *Expert Rev Anticancer Ther* 2008; 8: 175–81.
4. Fisher DR, *et al.* MIRD dose estimate report No. 20: radiation absorbed-dose estimates for ^{111}In- and ^{90}Y-ibritumomab tiuxetan. *J Nucl Med* 2009; 50: 644–52.
5. Bal CS, *et al.* Radiolabeled somatostatin analogs for radionuclide imaging and therapy in patients with gastroenteropancreatic neuroendocrine tumors. *Trop Gastroenterol* 2010; 31: 87–95.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to indium-111 since a very small amount of radioactivity has been reported to be present in breast milk for 20 hours.

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 01/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: OctreoScan; *Belg.*: OctreoScan; *Cz.*: OctreoScan; *Denm.*: OctreoScan; *Fin.*: OctreoScan; *Israel*: Prostascint Kit; *Ital.*: OctreoScan; *Neth.*: OctreoScan; *Port.*: OctreoScan; *Spain*: OctreoScan; *USA*: OctreoScan.

Multi-ingredient Preparations. *Irl.*: OctreoScan.

Pharmacopoeial Preparations
Ph. Eur.: Indium(^{111}In) Chloride Solution; Indium(^{111}In) Oxine Solution; Indium(^{111}In) Pentetate Injection;
USP 36: Indium In 111 Capromab Pentetide Injection; Indium In 111 Chloride Solution; Indium In 111 Ibritumomab Tiuxetan Injection; Indium In 111 Oxyquinoline Solution; Indium In 111 Pentetate Injection; Indium In 111 Pentetreotide Injection; Indium In 111 Satumomab Pendetide Injection.

Iodine-123

Iod-123; Iode-123; Iodio-123; Iodo 123; Jód-123; Jod-123; Jodi-123; Jodium-123; Yodo 123; Yod-123.

CAS — 15715-08-9 (iodine-123); 76924-93-1 (iobenguane (^{123}I)); 139755-80-9 (iobenguane (^{123}I) sulfate); 74855-17-7 (iocanlidic acid (^{123}I)); 54510-20-2 (iodocetylic acid (^{123}I)); 75917-92-9 (iofetamine (^{123}I)); 85068-76-4 (iofetamine (^{123}I) hydrochloride); 123748-56-1 (iodofiltic acid (^{123}I)); 155798-07-5 (ioflupane (^{123}I)); 113716-48-6 (iolopride (^{123}I)); 127396-36-5 (iomazenil (^{123}I)); 136794-86-0 (iometopane (^{123}I)); 41927-88-2 (sodium iodide (^{123}I)); 56254-07-0 (sodium iodohippurate (^{123}I)).

ATC — V09AB01 (iofetamine (123I)); V09AB02 (iodine iolopride (123I)); V09AB03 (iodine ioflupane (123I)); V09CX01 (sodium iodohippurate (123I)); V09FX02 (sodium iodide (123I)); V09IX01 (iobenguane (123I)).

ATC Vet — QV09AB01 (iofetamine (123I)); QV09AB02 (iodine iolopride (123I)); QV09AB03 (iodine ioflupane (123I)); QV09CX01 (sodium iodohippurate (123I)); QV09FX02 (sodium iodide (123I)); QV09IX01 (iobenguane (123I)).

UNII — 81WR746RPQ (iodine-123); P2TH1XYZB4 (iobenguane (^{123}I)); 23X1185WBO (iobenguane (^{123}I) sulfate); LV23B78UC (iofetamine (^{123}I)); 8SO1XB5L3M (iofetamine (^{123}I) hydrochloride); 097USQ749M (iodofiltic acid (^{123}I)); 3MM99TBR5Q (ioflupane (^{123}I)); 5E76SOO99K (iolopride (^{123}I)); BB51121553 (iomazenil (^{123}I)); Z19Y64M4R6 (iometopane (^{123}I)); 29UIX3A616 (sodium iodide (^{123}I)); 4NW20GFQ7H (sodium iodohippurate (^{123}I)).

NOTE. Iobenguane Sulfate I 123 is *USAN*.
Iocanlidic Acid (^{123}I) is *rINN* and Iocanlidic Acid I 123 is *USAN*.
Iodocetylic Acid (^{123}I) is *rINN* and Iodocetylic Acid I 123 is *USAN*.
Iodofiltic Acid (^{123}I) is *rINN* and Iodofiltic Acid I 123 is *USAN*.
Iodohippurate Sodium I 123 is *USAN*.
Iofetamine (^{123}I) is *rINN* and Iofetamine Hydrochloride I 123 is *USAN*.
Ioflupane (^{123}I) is *rINN*, Ioflupane[^{123}I] is *BAN*, and Ioflupane I 123 is *USAN*.
Iolopride (^{123}I) is *rINN*.
Iomazenil (^{123}I) is *rINN*.
Iometopane (^{123}I) is *rINN* and Iometopane I 123 is *USAN*.
HALF-LIFE. 13.3 hours.

Profile

Iodine-123 (^{123}I) is a radioactive isotope of iodine (p. 2336.3) that decays by electron capture with emission of X-rays (see Radioactive Decay, p. 2222.1). It has similar adverse effects and precautions to those of iodine-131 (see p. 2226.2).

Its principal use is in thyroid uptake tests and thyroid imaging when it is given orally or by intravenous injection as sodium iodide (^{123}I).

Sodium iodohippurate (^{123}I) is given intravenously in tests of renal function and in renal imaging.

Iobenguane (^{123}I) (*m*-iodobenzylguanidine (^{123}I)) is given intravenously for the localisation of certain tumours, for example phaeochromocytomas, and for the evaluation of neuroblastoma.

Ioflupane (^{123}I) is given intravenously to detect loss of functioning dopaminergic neurones in the differential diagnosis of tremor and parkinsonism. Iometopane (^{123}I) has been studied for the early diagnosis of parkinsonism.

Iomazenil (^{123}I), an analogue of flumazenil reported to have high affinity for central benzodiazepine receptors, has been used to study cerebrovascular diseases.

Iodofiltic acid (^{123}I) (BMIPP; *Zemiva*™) is being studied in the prognosis of coronary artery disease.

Various monoclonal antibodies have been labelled with iodine-123; potential applications include the detection of malignant neoplasms.

References.
1. Biswas SK, *et al.* 123I-BMIPP fatty acid analogue imaging is a novel diagnostic and prognostic approach following acute myocardial infarction. *Singapore Med J* 2009; 50: 943–8.
2. Inaba Y, Bergmann SR. Prognostic value of myocardial metabolic imaging with BMIPP in the spectrum of coronary artery disease: a systematic review. *J Nucl Cardiol* 2010; 17: 61–70.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to iodine-123 since radioactivity has been reported to be present in breast milk for up to 36 hours.

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 01/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: AdreView†; DaTSCAN†; MIBG; *Cz.*: DaTSCAN; Hippuran; MIBG; *Fin.*: MIBG; *Fr.*: AdreView; DaTSCAN; *Irl.*: DaTSCAN; *Israel*: DaTSCAN; *Ital.*: DaTSCAN; *Neth.*: AdreView; DaTSCAN; Hippuran; MIBG; *Pol.*: DaTSCAN; *Port.*: DaTSCAN; *Spain*: AdreView; DaTSCAN; MIBG; *Switz.*: AdreView; DaTSCAN; *UK*: AdreView; DaTSCAN; *USA*: AdreView; DaTSCAN.

Multi-ingredient Preparations. *Irl.*: MIBG.

Pharmacopoeial Preparations
Ph. Eur.: Sodium Iodide(^{123}I) Injection; Sodium Iodide(^{123}I) Solution for Radiolabelling; Sodium Iodohippurate(^{123}I) Injection;
USP 36: Iobenguane I 123 Injection; Iodohippurate Sodium I 123 Injection; Sodium Iodide I 123 Capsules; Sodium Iodide I 123 Solution.

Iodine-124

Iod-124; Iode-124; Iodio-124; Iodo-124; Jód-124; Jod-124; Jodi-124; Jodium-124; Yodo-124.

CAS — 14158-30-6 (iodine-124); 1011710-99-8 (iodine (^{124}I) girentuximab).

UNII — P0I0FT82VK (iodine (^{124}I) girentuximab).

NOTE. Iodine (^{124}I) Girentuximab is *rINN* and Iodine I 124 Girentuximab is *USAN*.
HALF-LIFE. 4.2 days.

Profile

Iodine-124 (^{124}I) is a radioactive isotope of iodine (p. 2336.3) that decays by electron capture and positron emission (see Radioactive Decay, p. 2222.1). It is used in positron-emission tomography for the imaging of thyroid tissue and is under investigation for the radiolabelling of various compounds, including the monoclonal antibody girentuximab (p. 802.3). Iodine (^{124}I) girentuximab (*Redectane*™) is being studied for imaging of renal tumours.

Iodine-125

Iod-125; Iode-125; Iodio-125; Iodo 125; Jód-125; Jod-125; Jodi-125; Jodium-125; Yodo 125.

CAS — 14158-31-7 (iodine-125); 17033-82-8 (iometin (^{125}I)); 24359-64-6 (sodium iodide (^{125}I)); 7230-65-1 (sodium iodohippurate (^{125}I)); 17692-74-9 (sodium iotalamate (^{125}I)).

ATC — V09CX02 (sodium iotalamate (125I)); V09GB01 (fibrinogen (125I)); V09GB02 (iodinated human albumin (125I)); V09IX03 (iodine CC49 monoclonal antibody (125I)).

ATC Vet — QV09CX03 (sodium iotalamate (125I)); QV09GB01 (fibrinogen (125I)); QV09GB02 (iodinated human albumin (125I)); QV09IX03 (iodine CC49 monoclonal antibody (125I)).

UNII — GVO77661TR (iodine-125); 68WOO3N91T (iodinated (^{125}I) human serum albumin); HXP39D7U8L (iometin (^{125}I)); HI3JK0W0I (sodium iodide (^{125}I)); T5536Q4O60 (sodium iodohippurate (^{125}I)); 33U5U3Q9ZN (sodium iotalamate (^{125}I)).

NOTE. Diohippuric Acid I 125 is *USAN*. Diotyrosine I 125 is *USAN*.
Fibrinogen (^{125}I) is *rINN* and Fibrinogen I 125 is *USAN*.
Iodinated (^{125}I) Human Serum Albumin is *rINN*.
Iodohippurate Sodium I 125 is *USAN*.
Iodopyracet I 125 is *USAN*.
Iometin (^{125}I) is *rINN* and Iomethin I 125 is *USAN*.
Rose Bengal Sodium I 125 is *USAN*.
Sodium Iodide (^{125}I) is *rINN* and Sodium Iodide I 125 is *USAN*.
Sodium Iotalamate (^{125}I) is *rINN* and Iothalamate Sodium I 125 is *USAN*.
HALF-LIFE. 59.4 days.

Profile

Iodine-125 (^{125}I) is a radioactive isotope of iodine (p. 2336.3) that decays by electron capture (see Radioactive Decay, p. 2222.1). It has similar adverse effects and precautions to those of iodine-131 (see p. 2226.2).

Iodine-125 is not very suitable for external detection after thyroid uptake because its gamma-energy is weak, and it is best reserved for *in vitro* applications. Sodium iodide (^{125}I) is used for radio-immunoassay kits and for iodination of compounds such as proteins.

Sodium iotalamate (^{125}I) is used intravenously in the determination of *GFR* in patients with renal disease.

Human albumin iodinated with iodine-125 is used for the determination of blood or plasma volume.

Iodine-125, as iodinated (^{125}I) human fibrinogen, has been used intravenously to demonstrate and locate deep-vein thrombosis of the leg. Iodinated (^{125}I) fibrinogen has also been used in the measurement of fibrinogen metabolism.

Iodine-125 implants are used for the local treatment of cancers (brachytherapy). Titanium capsules containing iodine-125 adsorbed onto a silver rod are used in the treatment of prostate cancer and other selected, localised tumours. It has also been used for intracavitary brachytherapy of malignant gliomas, where it is instilled into an inflatable balloon catheter.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to iodine-125 since radioactivity has been reported to be present in breast milk for 12 days.

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 01/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: OncoSeeds†; Rapid Strand†; *Switz.*: Seralb-I-125; *USA*: Glofil.

Pharmacopoeial Preparations
Ph. Eur.: Human Albumin Injection, Iodinated (^{125}I);
USP 36: Iodinated I 125 Albumin Injection; Iothalamate Sodium I 125 Injection.

Iodine-131

Iod-131; Iode-131; Iodio-131; Iodo 131; Jód-131; Jod-131; Jodi-131; Jodium-131; Yodo 131.

CAS — 10043-66-0 (iodine-131); 14679-68-6 (diotyrosine (^{131}I)); 77679-27-7 (iobenguane (^{131}I)); 149210-33-3 (iobenguane (^{131}I) sulfate); 24360-85-8 (iodipamide (^{131}I)); 3791-63-7 (iodoantipyrine (^{131}I)); 42220-21-3 (iodocholesterol (^{131}I)); 1214283-52-9 (ioflubenzamide (^{131}I)); 17033-83-9 (iometin (^{131}I)); 16624-40-1 (iotyrosine (^{131}I)); 54182-63-7 (macrosalb (^{131}I)); 24916-55-0 (rose bengal (^{131}I) sodium closed form); 50291-21-9 (rose bengal (^{131}I) sodium open form); 7790-26-3 (sodium iodide (^{131}I)); 881-17-4 (sodium iodohippurate (^{131}I)); 15845-98-4 (sodium iotalamate (^{131}I)); 9015-62-7 (tolpovidone (^{131}I)).

ATC — V09CX02 (sodium iodohippurate (131I)); V09FX03 (sodium iodide (131I)); V09IX02 (iobenguane (131I)); V09XA01 (iodine norcholesterol (131I)); V09XA02 (iodocholesterol (131I)); V09XA03 (iodinated human albumin (131I)); V10XA01 (sodium iodide (131I)); V10XA02 (iobenguane (131I)); V10XA53 (iodine tositumomab (131I)).

ATC Vet — QV09CX02 (sodium iodohippurate (^{131}I)); QV09FX03 (sodium iodide (^{131}I)); QV09IX02 (iobenguane (^{131}I)); QV09XA01 (iodine norcholesterol (^{131}I)); QV09XA02 (iodocholesterol (^{131}I)); QV09XA03 (iodinated human albumin (^{131}I)); QV10XA01 (sodium iodide (^{131}I)); QV10XA02 (iobenguane (^{131}I)); QV10XA53 (iodine tositumomab (^{131}I)).

UNII — I5X6L61HUT (iodine-131); 4GC1FOQ22U (iodine-131 ion); Q461L7AK4R (iobenguane (^{131}I)); M575VKV19N (iobenguane (^{131}I) sulfate); ACH35131L1 (iodinated (^{131}I) human serum albumin); K1KT5M40JC (iodine (^{131}I) tositumomab); QR6HQ1U73Z (iodoantipyrine (^{131}I)); C5F4248GPJ (iodocholesterol (^{131}I)); POY4SKT67X (iometin (^{131}I)); Q1M94GA18P (iotyrosine (^{131}I)); 24I7KUI7MK (rose bengal (^{131}I) sodium); 29VCO8ACHH (sodium iodide (^{131}I)); 9BRV734R3E (sodium iodohippurate (^{131}I)).

NOTE. Diohippuric Acid I 131 is *USAN*.
Diotyrosine I 131 is *USAN*.
Ethiodized Oil (^{131}I) is *rINN* and Ethiodized Oil I 131 is *USAN*.
Iobenguane (^{131}I) is *rINN* and Iobenguane I 131 is *USAN*.
Iobenguane Sulfate I 131 is *USAN*.
Iodinated (^{131}I) Human Serum Albumin is *rINN*.
Iodipamide Sodium I 131 is *USAN*.
Iodoantipyrine I 131 is *USAN*.
Iodocholesterol (^{131}I) is *rINN* and Iodocholesterol I 131 is *USAN*.
Iodopyracet I 131 is *USAN*.
Ioflubenzamide (^{131}I) is *rINN*.
Iometin (^{131}I) is *rINN* and Iomethin I 131 is *USAN*.
Iotyrosine I 131 is *USAN*.
Macrosalb (^{131}I) is *rINN* and *BAN*.
Rose Bengal (^{131}I) Sodium is *rINN* and Rose Bengal Sodium I 131 is *USAN*.
Sodium Iodide (^{131}I) is *rINN* and Sodium Iodide I 131 is *USAN*.
Sodium Iodohippurate (^{131}I) is *rINN* and Iodohippurate Sodium I 131 is *USAN*.
Sodium Iotalamate (^{131}I) is *rINN* and Iothalamate Sodium I 131 is *USAN*.
Tolpovidone (^{131}I) is *rINN* and Tolpovidone I 131 is *USAN*.
HALF-LIFE. 8.02 days.

Uses and Administration

Iodine-131 (^{131}I) is a radioactive isotope of iodine (p. 2336.3) that decays by beta and gamma emission (see Radioactive Decay, p. 2222.1). It is mainly used in studies of thyroid function and in the treatment of hyperthyroidism (p. 2332.2) and some forms of thyroid carcinoma (p. 716.1). It is common practice to saturate the thyroid with non-radioactive iodine when uptake of radiation by the gland is not desired (see Radiation Protection, p. 2338.1).

Sodium iodide (^{131}I) is given orally and by intravenous injection in studies of thyroid function, particularly in measurements of the uptake of iodine by the thyroid, and in thyroid scanning. It is also used in the treatment of hyperthyroidism and in the treatment of malignant neoplasms of the thyroid.

Iodine radioisotopes can be incorporated into many other compounds, for various diagnostic and therapeutic purposes.

Injections containing iobenguane (^{131}I) (*m*-iodobenzylguanidine (^{131}I)) may be used for the localisation and treatment of phaeochromocytoma (p. 1278.1), neuroblastoma (p. 716.2), and thyroid gland carcinoma.

Iodinated (^{131}I) norcholesterol (6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (^{131}I)) has been used for adrenal scintigraphy by slow intravenous injection.

Various monoclonal antibodies labelled with iodine-131 are used for the detection of malignant neoplasms and some are used for therapeutic purposes, such as iodine (^{131}I) tositumomab (p. 874.2) for non-Hodgkin's lymphoma. Fatty acids may be iodinated with radioactive iodine and used for the treatment of unresectable malignant neoplasms of the liver.

Human albumin iodinated with iodine-131 was used in the determination of CSF dynamics, protein losing enteropathy, and for liver imaging but its use has been superseded by other radiopharmaceuticals.

Sodium iodohippurate (^{131}I) was used intravenously for renal-function tests and for renal imaging.

Rose bengal sodium (^{131}I) has been given intravenously in tests of liver function.

References.
1. Van Nostrand D. The benefits and risks of I-131 therapy in patients with well-differentiated thyroid cancer. *Thyroid* 2009; 19: 1381–91.
2. Araujo F, *et al.* Optimization of (131)I doses for the treatment of hyperthyroidism. *Cell Mol Biol (Noisy-le-grand)* 2009; 55: 1–6.
3. Lassmann M, *et al.* Dosimetry and thyroid cancer: the individual dosage of radioiodine. *Endocr Relat Cancer* 2010; 17: R161–R172.

Adverse Effects and Treatment

Therapy with iodine-131 may temporarily exacerbate existing hyperthyroidism, and can precipitate thyroid storm (see Hyperthyroidism, p. 2332.2). Dose-dependent hypothyroidism may occur as a late consequence, occurring weeks or years after treatment, and requiring thyroid replacement therapy. However, this hypothyroidism may also be transient, and replacement therapy should not be started too early. Both hyperparathyroidism and hypoparathyroidism have been reported. High doses, such as those used to treat thyroid cancer, can cause radiation thyroiditis resulting in swelling and localised pain; this may cause tracheal constriction and rarely, respiratory distress. This can subside spontaneously or may need corticosteroid treatment. Sialadenitis (inflammation of the salivary glands) can occur, causing loss of taste and dry mouth. While it usually subsides spontaneously, anti-inflammatory treatment may be required, and there are reports of persistent symptoms leading to tooth loss. Gastrointestinal disturbances are common with radio-iodine, especially after oral use, and usually occur within the first hours or days after ingestion. Bone marrow depression, with isolated thrombocytopenia or erythrocytopenia, may occur after a high dose. Although this is usually reversible, it may sometimes be irreversible or fatal.

Although the use of radio-iodine for hyperthyroidism is not generally considered to increase the risk of malignancy, there have been some reports of an increased incidence of cancers including those of bladder, breast, and stomach, after radio-iodine therapy, and high-dose treatment may increase the risk of leukaemia.

Hypersensitivity reactions can occur with iodine (see also under Iodine, p. 2338.2).

References.
1. Ron E, *et al.* Cancer mortality following treatment for adult hyperthyroidism. *JAMA* 1998; 280: 347–55.
2. Franklyn JA, *et al.* Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet* 1999; 353: 2111–15.
3. Rivkees SA, Cornelius EA. Influence of iodine-131 dose on the outcome of hyperthyroidism in children. *Pediatrics* 2003; 111: 745–9.

Precautions

The use of sodium iodide (^{131}I) is contra-indicated, even in diagnostic doses, during pregnancy. It should also not be used for diagnostic purposes in children younger than 10 years of age. Sodium iodide (^{131}I) is not recommended for thyroid scanning except in the follow-up of malignant disease, or where iodine-123 or technetium-99m are not available. There is some controversy as to whether radio-iodine therapy exacerbates Graves' ophthalmopathy (see Hyperthyroidism, p. 2332.2). Sodium iodide (^{131}I) is contra-indicated in patients with dysphagia, oesophageal stricture, active gastritis, gastric erosions, peptic ulceration, or reduced gastrointestinal motility. Caution is advised in patients with renal impairment.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to iodine-131 since radioactivity has been reported to be present in breast milk for 2 to 14 days; high doses used for the treatment of thyroid cancer may prolong exposure to the infant.

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 01/07/04)

Interactions

Many drugs interact with radio-iodine; mechanisms vary but can affect protein binding, pharmacokinetics, or the uptake of iodine-131. Licensed product information recommends that the following drugs be withdrawn before use of sodium iodide (^{131}I):

- antithyroid drugs e.g. carbimazole, thiamazole, propylthiouracil, or perchlorates: withdrawn 2 to 7 days before use and withheld until several days after use
- salicylates, corticosteroids, sodium nitroprusside, sulfobromophthalein sodium, anticoagulants, antihistamines, antibacterials such as penicillins or sulfonamides or rifampicin, amphotericin B, tiabendazole, tolbutamide, thiopental: withdrawn 1 week before use
- iodine-containing preparations for systemic use such as vitamins or expectorants: withdrawn 2 weeks before use
- iodine-containing preparations for topical use: withdrawn 1 to 9 months before use
- iodine-containing contrast media: withdrawn up to 1 year before use
- thyroid hormone preparations: withdrawn 2 to 6 weeks before use
- amiodarone, benzodiazepines, lithium: withdrawn about 4 weeks before use

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Curicap; Theracap†; *Canad.*: Bexxar; *China*: Li Ka Ting (利卡汀); Wei Mei Sheng (唯美生); *Cz.*: Capsion; Curicap; Theracap; *Denm.*: Theracap; *Fin.*: Theracap; *Fr.*: Capsion; Lipiocis†; Theracap; *Israel*: Theracap; *Neth.*: Capsion; Curicap†; Jobenguaan†; Theracap; *Port.*: Capsion; Curicap; Theracap; *Spain*: Capsion; Curicap; Theracap; *Switz.*: Theracap; *UK*: Capsion; Theracap; *USA*: Bexxar; Hicon; Iodotope†.

Pharmacopoeial Preparations
Ph. Eur.: Iobenguane(^{131}I) Injection for Diagnostic Use; Iobenguane(^{131}I) Injection for Therapeutic Use; Iodinated(^{131}I) Norcholesterol Injection; Sodium Iodide(^{131}I) Capsules for Diagnostic Use; Sodium Iodide(^{131}I) Capsules for Therapeutic Use; Sodium Iodide(^{131}I) Solution for Radiolabelling; Sodium Iodide(^{131}I) Solution; Sodium Iodohippurate(^{131}I) Injection;
USP 36: Iobenguane I 131 Injection; Iodinated I 131 Albumin Aggregated Injection; Iodinated I 131 Albumin Injection; Iodohippurate Sodium I 131 Injection; Rose Bengal Sodium I 131 Injection; Sodium Iodide I 131 Capsules; Sodium Iodide I 131 Solution.

Krypton-81m

Criptón 81m; Cripton-81m; Kripton-81m; Krypton Kr 81m (USAN); Криптон-81м.

CAS — 15678-91-8.

ATC — V09EX01 (krypton gas (^{81m}Kr)).

ATC Vet — QV09EX01 (krypton gas (^{81m}Kr)).

UNII — 68QN45K12N.

HALF-LIFE. 13.1 seconds.

Profile

Krypton-81m (^{81m}Kr) decays by isomeric transition and emits gamma rays (see Radioactive Decay, p. 2222.1). It is a daughter of rubidium-81 (^{81}Rb, half-life 4.58 hours), and is prepared immediately before use by elution from a generator containing rubidium-81 adsorbed on a suitable ion-exchange column using air or oxygen as the eluent. Krypton-81m is used as a gas in lung ventilation studies. Such ventilation studies can be combined with lung perfusion studies to diagnose pulmonary embolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: KryptoScan; *Irl.*: KryptoScan; *Neth.*: KryptoScan.

Pharmacopoeial Preparations
Ph. Eur.: Krypton(^{81m}Kr) Inhalation Gas;
USP 36: Krypton Kr 81m.

Nitrogen-13

Azot-13; Azote-13; Azoto-13; Dusík-13; Köfnunarefni-13; Kvāve-13; Kvælstof-13; Nitrogén-13; Nitrógeno 13; Stickstoff-13; Stikstof-13; Typpi-13; Азот-13.

CAS — 13981-22-1.

HALF-LIFE. 9.96 minutes.

Profile

Nitrogen-13 (^{13}N) is a radioactive isotope of nitrogen (p. 1799.3) that emits positrons. It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1). In the form of ammonia (^{13}N) it is given intravenously for imaging blood flow in organs such as the heart. Nitrogen gas (^{13}N) may be used for pulmonary ventilation and perfusion studies.

References.
1. Hove JD, *et al.* Simultaneous cardiac output and regional myocardial perfusion determination with PET and nitrogen 13 ammonia. *J Nucl Cardiol* 2003; 10: 28–33.
2. Hove JD, *et al.* Left atrial versus left ventricular input function for quantification of the myocardial blood flow with nitrogen-13 ammonia and positron emission tomography. *Eur J Nucl Med Mol Imaging* 2004; 31: 71–6.
3. Kumar R, *et al.* Production of nitrogen-13-labeled ammonia by using 11MeV medical cyclotron: our experience. *Hell J Nucl Med* 2009; 12: 248–50.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Ammonia(^{13}N) Injection;
USP 36: Ammonia N 13 Injection.

Oxygen-15

Happi-15; Ilt-15; Kyslík-15; Oksygen-15; Ossigeno-15; Oxigen-15; Oxigénio-15; Oxígeno 15; Oxygène-15; Sauerstoff-15; Súrefni-15; Syre-15; Tlen-15; Zuurstof-15; Кислород-15.

CAS — 13982-43-9 (oxygen-15); 24286-21-3 (water (^{15}O)).
UNII — 63M8RYN44N (water (^{15}O)).

NOTE. Water O 15 is *USAN*.
HALF-LIFE. 122.2 seconds.

Profile

Oxygen-15 (^{15}O) is a radioactive isotope of oxygen (p. 1799.3) that emits positrons. It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1). It is used in the form of water (^{15}O) and is given intravenously to study cerebral and myocardial perfusion.

Oxygen gas, carbon dioxide, and carbon monoxide have also been labelled with oxygen-15.

References.

1. Koh T, *et al.* Oxygen-15 positron-emission tomography for predicting selective delivery of a chemotherapeutic agent to hepatic cancers during angiotensin II-induced hypertension. *Cancer Chemother Pharmacol* 2003; 51: 349–58.
2. van den Heuvel OA, *et al.* Amygdala activity in obsessive-compulsive disorder with contamination fear: a study with oxygen-15 water positron emission tomography. *Psychiatry Res* 2004; 132: 225–37.
3. Iwanishi K, *et al.* Influence of residual oxygen-15-labeled carbon monoxide radioactivity on cerebral blood flow and oxygen extraction fraction in a dual-tracer autoradiographic method. *Ann Nucl Med* 2009; 23: 363–71.
4. Luurtsema G, *et al.* Pharmaceutical preparation of oxygen-15 labelled molecular oxygen and carbon monoxide gasses in a hospital setting. *J Clin Pharm Ther* 2010; 35: 63–9.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Carbon Monoxide(^{15}O); Oxygen(^{15}O); Water(^{15}O) Injection;
USP 36: Water O 15 Injection.

Phosphorus-32

Fosfor-32; Fosfór-32; Fosfori-32; Fósforo 32; Fosforo-32; Foszfor-32; Phosphor-32; Phosphore-32; Фосфор-32.
CAS — 14596-37-3 (phosphorus-32); 24381-60-0 (chromic phosphate (^{32}P)); 7635-46-3 (sodium phosphate (^{32}P)).
ATC — V10AX01 (phosphorus chromic phosphate colloid (^{32}P)); V10XX01 (sodium phosphate (^{32}P)).
ATC Vet — QV10AX01 (phosphorus chromic phosphate colloid (^{32}P)); QV10XX01 (sodium phosphate (^{32}P)).
UNII — 690284A407 (phosphorus-32); QHO02LZ4H2 (chromic phosphate (^{32}P)); O181101B5G (sodium phosphate (^{32}P)).

NOTE. Chromic Phosphate P 32 is *USAN*.
Sodium Phosphate (^{32}P) is *rINN* and Sodium Phosphate P 32 is *USAN*.
HALF-LIFE. 14.3 days.

Profile

Phosphorus-32 (^{32}P) is a radioactive isotope of phosphorus (p. 2589.2) that decays by beta emission (see Radioactive Decay, p. 2222.1). Given as sodium phosphate (^{32}P), it is used intravenously in the treatment of polycythaemia vera (p. 695.2). Phosphorus-32 is taken up by the rapidly proliferating haematopoietic cells sufficiently to reduce their reproduction. Sodium phosphate (^{32}P) has also been used intravenously in the treatment of chronic myeloid (p. 694.2) and chronic lymphocytic leukaemia (p. 693.3) and in the palliative treatment of bone metastases (p. 700.3).

Chromic phosphate (^{32}P) has been given intraperitoneally or intrapleurally in the treatment of malignant effusions (p. 700.1); it has also been given by interstitial injection for the treatment of ovarian (p. 711.2) or prostatic carcinoma (p. 712.3). Intra-articular injection into the synovial joint space has been used for the treatment of diseases such as rheumatoid arthritis and arthropathies (radiation synovectomy).

References.

1. Parmentier C. Use and risks of phosphorus-32 in the treatment of polycythaemia vera. *Eur J Nucl Med Mol Imaging* 2003; 30: 1413–17.
2. Hasegawa T, *et al.* Management of cystic craniopharyngiomas with phosphorus-32 intracavitary irradiation. *Neurosurgery* 2004; 54: 813–20.
3. Vinjamuri S, Ray S. Phosphorus-32: the forgotten radiopharmaceutical? *Nucl Med Commun* 2008; 29: 95–7.
4. Zhao R, *et al.* Treatment of cystic craniopharyngioma with phosphorus-32 intracavitary irradiation. *Childs Nerv Syst* 2010; 26: 669–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Phosphocol†.

Pharmacopoeial Preparations
Ph. Eur.: Sodium Phosphate(^{32}P) Injection;
USP 36: Chromic Phosphate P 32 Suspension; Sodium Phosphate P 32 Solution.

Radium-223

BAY-88-8223 (radium (223Ra) chloride); Raadium-223; Rad-223; Radi-223; Radij-223; Radijs-223; Radijum-223; Radin-223; Radio-223; Rádio-223; Radis-223; Rádium-223; Radiwm-223; Radyum-223; Raidiam-223; Радий-223.
CAS — 15623-45-7 (radium-223); 444811-40-9 (radium (^{223}Ra) chloride).

NOTE. Radium Ra 223 Dichloride is *USAN*.
The name Alpharadin has been used as a trade mark for radium-223 chloride.
HALF-LIFE. 11.4 days.

Profile

Radium-223 (^{223}Ra) is a radioactive isotope of radium that emits alpha particles (see Radioactive Decay, p. 2222.1). Radium (^{223}Ra) chloride is given intravenously for the treatment of bone metastases in patients with castration-resistant prostate cancer (p. 712.3).

References.

1. Harrison MR, *et al.* Radium-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease. *Cancer Manag Res* 2013; 5: 1–14.
2. Joung JY, *et al.* Radium Ra 223 dichloride in castration-resistant prostate cancer. *Drugs Today* 2013; 49: 483–90.
3. Parker C, *et al.* ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; 369: 213–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Xofigo; *USA*: Xofigo.

Rhenium-186

Ren-186; Renin-186; Renio 186; Renio-186; Rênio-186; Renjum-186; Rénium-186; Rhénium-186; Рений-186.
CAS — 14998-63-1.
ATC — V10AX05 (rhenium sulfide colloid (^{186}Re)); V10BX03 (rhenium etidronate (^{186}Re)).
ATC Vet — QV10AX05 (rhenium sulfide colloid (^{186}Re)); QV10BX03 (rhenium etidronate (^{186}Re)).

HALF-LIFE. 89.2 hours.

Profile

Rhenium-186 (^{186}Re) is a radioactive isotope of rhenium that decays by beta and gamma emission (see Radioactive Decay, p. 2222.1). It has been used in the form of a colloidal sulfide, as an imaging agent and for the treatment of arthritic joint conditions. Rhenium (^{186}Re) etidronate is used for the palliation of painful bone metastases (p. 700.3) of prostate cancer. Monoclonal antibodies labelled with rhenium-186 have been investigated for the treatment of various malignant neoplasms.

References.

1. Han SH, *et al.* 186Re-etidronate: efficacy of palliative radionuclide therapy for painful bone metastases. *Q J Nucl Med* 2001; 45: 84–90.
2. Liu G, Hnatowich DJ. Labeling biomolecules with radiorhenium: a review of the bifunctional chelators. *Anticancer Agents Med Chem* 2007; 7: 367–77.
3. Kleu R, *et al.* Radiosynoviorthesis of medium-sized joints with rhenium-186-sulphide colloid: a review of the literature. *Rheumatology (Oxford)* 2007; 46: 1531–7.
4. van der Zant FM, *et al.* Radiation synovectomy with (90)Yttrium, (186) Rhenium and (169)Erbium: a systematic literature review with meta-analyses. *Clin Exp Rheumatol* 2009; 27: 130–9.
5. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010; 40: 89–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: RE-186-MM-1; Re-Bone†; *Fr.*: Nanocis; *Irl.*: Nanocis.

Rhenium-188

Ren-188; Renin-188; Renio-188; Rênio-188; Renium-188; Rénium-188; Rhénium-188; Рений-188.
CAS — 14378-26-8.

HALF-LIFE. 16.98 hours.

Profile

Rhenium-188 (^{188}Re) is a radioactive isotope of rhenium that decays by beta and gamma emission (see Radioactive Decay, p. 2222.1). It has been used to label antibody fragments. Rhenium (^{188}Re) etidronate is used for the palliation of painful bone metastases (p. 700.3). Iodised oil labelled with rhenium-188 is used intra-arterially for the treatment of liver tumours. A rhenium-188-filled balloon catheter has also been used for recurrent restenosis.

References.

1. Klein SA, *et al.* Transplantation-related toxicity and acute intestinal graft-versus-host disease after conditioning regimens intensified with rhenium 188-labeled anti-CD66 monoclonal antibodies. *Blood* 2002; 99: 2270–1.
2. Scheffler J, *et al.* Application of rhenium-188 HEDP in bone metastases therapy. *Nucl Med Rev Cent East Eur* 2003; 6: 55–7.
3. Wöhrle J, *et al.* Intracoronary β-brachytherapy using a rhenium-188 filled balloon catheter in restenotic lesions of native coronary arteries and venous bypass grafts. *Eur J Nucl Med Mol Imaging* 2006; 33: 1314–20.
4. Zanzonico PB, Divgi C. Patient-specific radiation dosimetry for radionuclide therapy of liver tumors with intrahepatic artery rhenium-188 lipiodol. *Semin Nucl Med* 2008; 38: S30–S39.
5. Bernal P, *et al.* International Atomic Energy Agency-sponsored multination study of intra-arterial rhenium-188-labeled lipiodol in the treatment of inoperable hepatocellular carcinoma: results with special emphasis on prognostic value of dosimetric study. *Semin Nucl Med* 2008; 38: S40–S45.
6. Lambert B, *et al.* Rhenium-188 based radiopharmaceuticals for treatment of liver tumours. *Q J Nucl Med Mol Imaging* 2009; 53: 305–10.
7. Shamim SA, *et al.* Role of rhenium-188 tin colloid radiosynovectomy in patients with inflammatory knee joint conditions refractory to conventional therapy. *Nucl Med Commun* 2010; 31: 814–20.

Rubidium-82

Rubid-82; Rubidin-82; Rubidio; Rubidio 82; Rubidium-82; Рубидий-82.
CAS — 14391-63-0 (rubidium-82); 132486-03-4 (rubidium (^{82}Rb) chloride).
UNII — 9K730EL8KU (rubidium-82); F0Z746KRKQ (rubidium (^{82}Rb) chloride).

NOTE. Rubidium Chloride Rb 82 is *USAN*.
HALF-LIFE. 75 seconds.

Profile

Rubidium-82 (^{82}Rb) is a radioactive isotope of rubidium that emits positrons. It is a daughter nuclide of strontium-82 (^{82}Sr). It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1). Rubidium chloride (^{82}Rb) is given intravenously for cardiac imaging to assess myocardial perfusion and heart function.

Preparations

Pharmacopoeial Preparations
USP 36: Rubidium Chloride Rb 82 Injection.

Samarium-153

Samario 153; Samario-153; Samário-153; Szamárium-153; Самарий-153.
CAS — 15766-00-4 (samarium-153); 154427-83-5 (samarium (^{153}Sm) lexidronam); 160369-78-8 (samarium (^{153}Sm) lexidronam pentasodium).
ATC — V10AX02 (samarium hydroxyapatite colloid (^{153}Sm)); V10BX02 (samarium lexidronam (^{153}Sm)).
ATC Vet — QV10AX02 (samarium hydroxyapatite colloid (^{153}Sm)); QV10BX02 (samarium lexidronam (^{153}Sm)).
UNII — 6Q1KA41UWM (samarium-153); 7389YR3OOV (samarium (^{153}Sm) lexidronam pentasodium).

NOTE. Samarium (^{153}Sm) Lexidronam is *rINN* and Samarium Sm 153 Lexidronam is *USAN*.
Samarium (^{153}Sm) Lexidronam Pentasodium is *rINNM* and Samarium Sm 153 Lexidronam Pentasodium is *USAN*.
HALF-LIFE. 46.3 hours.

Profile

Samarium-153 (^{153}Sm) is a radioactive isotope of samarium that emits beta and gamma radiation (see Radioactive Decay, p. 2222.1). Samarium (^{153}Sm) lexidronam (samarium (^{153}Sm) EDTMP) is given intravenously as the pentasodium for the palliative treatment of painful bone metastases (p. 700.3).

References.

1. Sartor O, *et al.* Samarium-153-lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* 2004; 63: 940–5.
2. Finlay IG, *et al.* Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol* 2005; 6: 392–400.
3. Anderson P. Samarium for osteoblastic bone metastases and osteosarcoma. *Expert Opin Pharmacother* 2006; 7: 1475–86.
4. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010; 40: 89–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Quadramet; *Fr.*: Quadramet; *Irl.*: Quadramet; *Ital.*: Quadramet; *Neth.*: Quadramet; *Pol.*: Quadramet; *Port.*: Quadramet; *Spain*: Quadramet; *Switz.*: Quadramet; *UK*: Quadramet; *USA*: Quadramet.

Pharmacopoeial Preparations
USP 36: Samarium Sm 153 Lexidronam Injection.

Selenium-75

Seleen-75; Seleeni-75; Selen-75; Selenio 75; Selênio-75; Sélénium-75; Szelén-75; Селен-75.
CAS — 14265-71-5 (selenium-75); 1187-56-0 (selenomethionine (^{75}Se)).
ATC — V09DX01 (selenium tauroselcholic acid (^{75}Se)); V09XX03 (selenium norcholesterol (^{75}Se)).
ATC Vet — QV09DX01 (selenium tauroselcholic acid (^{75}Se)); QV09XX03 (selenium norcholesterol (^{75}Se)).
UNII — 0X5608YSTZ (dl-selenomethionine (^{75}Se)); P6708E7555 (l-selenomethionine (^{75}Se)).

NOTE. Selenomethionine (^{75}Se) is *rINN* and Selenomethionine Se 75 is *USAN*.
HALF-LIFE. 119.8 days.

Profile

Selenium-75 (^{75}Se) is a radioactive isotope of selenium (p. 2086.3) that emits gamma radiation (see Radioactive Decay, p. 2222.1). Tauroselcholic acid (^{75}Se) (^{75}SeHCAT) is used orally in the measurement of bile acid absorption for the assessment of ileal function.

Selenium-75 in the form of 6β-[(methyl[^{75}Se]seleno)methyl]-19-norcholest-5(10)-en-3β-ol (selenonorcholesterol (^{75}Se)) has been used intravenously in adrenal scintigraphy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: SeHCAT†; *Denm.*: SeHCAT; *Fin.*: SeHCAT; *Irl.*: SeHCAT; *Neth.*: SeHCAT; *Spain*: SeHCAT; *UK*: Scintadren; SeHCAT.

Strontium-89

Estroncio 89; Estrôncio-89; Stroncium-89; Stront-89; Strontin-89; Stronzio-89; Стронций-89.
CAS — 14158-27-1 (strontium-89); 38270-90-5 (strontium (^{89}Sr) chloride).
ATC — V10BX01 (strontium chloride (^{89}Sr)).
ATC Vet — QV10BX01 (strontium chloride (^{89}Sr)).
UNII — 06A33308KH (strontium-89 ion); 5R78837D4A (strontium chloride (^{89}Sr)).

NOTE. Strontium Chloride Sr 89 is *USAN*.
HALF-LIFE. 50.5 days.

Profile

Strontium-89 (^{89}Sr) is a radioactive isotope of strontium that decays by beta emission (see Radioactive Decay, p. 2222.1). Strontium chloride (^{89}Sr) is given intravenously for the palliation of pain in patients with bone metastases (p. 700.3).

References.

1. Robinson RG, *et al.* Strontium 89 therapy for the palliation of pain due to osseous metastases. *JAMA* 1995; **274:** 420–4.
2. Giammarile F, *et al.* Bone pain palliation with strontium-89 in cancer patients with bone metastases. *Q J Nucl Med* 2001; **45:** 78–83.
3. Finlay IG, *et al.* Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol* 2005; **6:** 392–400.
4. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010; **40:** 89–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Metastron; *Belg.*: Metastron†; *Cz.*: Metastron; *Denm.*: Metastron; *Fin.*: Metastron; *Fr.*: Metastron; *Irl.*: Metastron; *Israel*: Metastron; *Ital.*: Metastron; *Neth.*: Metastron; *Port.*: Metastron; *Spain*: Metastron; *Switz.*: Metastron; *UK*: Metastron; *USA*: Metastron.

Pharmacopoeial Preparations
Ph. Eur.: Strontium(^{89}Sr) Chloride Injection;
USP 36: Strontium Chloride Sr 89 Injection.

Technetium-99m

Technécium-99m; Technecium-99m; Technet-99m; Technétium-99m; Tecnecio 99m; Tecnécio-99m; Tecnezio-99m; Teknetin-99m; Teknetium-99m; Технеций-99m.
CAS — 14133-76-7 (technetium-99); 154361-49-6 (arcitumomab (^{99m}Tc)); 54277-47-3 (macrosalb (^{99m}Tc)); 178959-14-3 (technetium (^{99m}Tc) apcitide); 121281-41-2 (technetium (^{99m}Tc) bicisate); 479410-20-3 (technetium (^{99m}Tc) etarfolatide); 105613-48-7 (technetium (^{99m}Tc) exametazime); 225239-31-6 (technetium (^{99m}Tc) fanolesomab); 142481-95-6 (technetium (^{99m}Tc) furifosmin); 125224-05-7 (technetium (^{99m}Tc) mertiatide); 131608-78-1 (technetium (^{99m}Tc) nitridocade); 165942-79-0 (technetium (^{99m}Tc) nofetumomab merpentan); 65454-61-7 (technetium (^{99m}Tc) pentetate); 157476-76-1 (technetium (^{99m}Tc) pintumomab); 109581-73-9 (technetium (^{99m}Tc) sestamibi); 106417-28-1 (technetium (^{99m}Tc) siboroxime); 7704-34-9 (technetium (^{99m}Tc) sulfur colloid); 104716-22-5 (technetium (^{99m}Tc) teboroxime); 104348-91-6 (technetium (^{99m}Tc) tiatide anion); 1262984-82-6 (technetium (^{99m}Tc) tilmanocept).
ATC — V09AA01 (technetium exametazime (^{99m}Tc)); V09AA02 (technetium bicisate (^{99m}Tc)); V09BA01 (technetium oxidronate (^{99m}Tc)); V09BA02 (technetium medronate (^{99m}Tc)); V09BA03 (technetium pyrophosphate (^{99m}Tc)); V09BA04 (technetium butedronate (^{99m}Tc)); V09CA01 (technetium pentetate (^{99m}Tc)); V09CA02 (technetium succimer (^{99m}Tc)); V09CA03 (technetium mertiatide (^{99m}Tc)); V09CA04 (technetium gluceptate (^{99m}Tc)); V09CA05 (technetium gluconate (^{99m}Tc)); V09CA06 (technetium ethylenedicysteine (^{99m}Tc)); V09DA01 (technetium disofenin (^{99m}Tc)); V09DA02 (technetium etifenin (^{99m}Tc)); V09DA03 (technetium lidofenin (^{99m}Tc)); V09DA04 (technetium mebrofenin (^{99m}Tc)); V09DA05 (technetium galtifenin (^{99m}Tc)); V09DB01 (technetium nanocolloid (^{99m}Tc)); V09DB02 (technetium microcolloid (^{99m}Tc)); V09DB03 (technetium millimicrospheres (^{99m}Tc)); V09DB04 (technetium tin colloid (^{99m}Tc)); V09DB05 (technetium sulfur colloid (^{99m}Tc)); V09DB06 (technetium rhenium sulfide colloid (^{99m}Tc)); V09DB07 (technetium phytate (^{99m}Tc)); V09EA01 (technetium pentetate (^{99m}Tc)); V09EA02 (technetium technegas (^{99m}Tc)); V09EA03 (technetium nanocolloid (^{99m}Tc)); V09EB01 (technetium macrosalb (^{99m}Tc)); V09EB02 (technetium microspheres (^{99m}Tc)); V09FX01 (technetium pertechnetate (^{99m}Tc)); V09GA01 (technetium sestamibi (^{99m}Tc)); V09GA02 (technetium tetrofosmin (^{99m}Tc)); V09GA03 (technetium teboroxime (^{99m}Tc)); V09GA04 (technetium human albumin (^{99m}Tc)); V09GA05 (technetium furifosmin (^{99m}Tc)); V09GA06 (technetium stannous agent labelled cells (^{99m}Tc)); V09GA07 (technetium apcitide (^{99m}Tc)); V09HA01 (technetium human immunoglobulin (^{99m}Tc)); V09HA02 (technetium exametazime labelled cells (^{99m}Tc)); V09HA03 (technetium antigranulocyte antibody (^{99m}Tc)); V09HA04 (technetium sulesomab (^{99m}Tc)); V09IA01 (technetium antiCEA antibody (^{99m}Tc)); V09IA02 (technetium antimelanoma antibody (^{99m}Tc)); V09IA03 (technetium pentavalent succimer (^{99m}Tc)); V09IA04 (technetium votumumab (^{99m}Tc)); V09IA05 (technetium depreotide (^{99m}Tc)); V09IA06 (technetium arcitumomab (^{99m}Tc)).
ATC Vet — QV09AA01 (technetium exametazime (^{99m}Tc)); QV09AA02 (technetium bicisate (^{99m}Tc)); QV09BA01 (technetium oxidronate (^{99m}Tc)); QV09BA02 (technetium medronate (^{99m}Tc)); QV09BA03 (technetium pyrophosphate (^{99m}Tc)); QV09BA04 (technetium butedronate (^{99m}Tc)); QV09CA01 (technetium pentetate (^{99m}Tc)); QV09CA02 (technetium succimer (^{99m}Tc)); QV09CA03 (technetium mertiatide (^{99m}Tc)); QV09CA04 (technetium gluceptate (^{99m}Tc)); QV09CA05 (technetium gluconate (^{99m}Tc)); QV09CA06 (technetium ethylenedicysteine (^{99m}Tc)); QV09DA01 (technetium disofenin (^{99m}Tc)); QV09DA02 (technetium etifenin (^{99m}Tc)); QV09DA03 (technetium lidofenin (^{99m}Tc)); QV09DA04 (technetium mebrofenin (^{99m}Tc)); QV09DA05 (technetium galtifenin (^{99m}Tc)); QV09DB01 (technetium nanocolloid (^{99m}Tc)); QV09DB02 (technetium microcolloid (^{99m}Tc)); QV09DB03 (technetium millimicrospheres (^{99m}Tc)); QV09DB04 (technetium tin colloid (^{99m}Tc)); QV09DB05 (technetium sulfur colloid (^{99m}Tc)); QV09DB06 (technetium rhenium sulfide colloid (^{99m}Tc)); QV09DB07 (technetium phytate (^{99m}Tc)); QV09EA01 (technetium pentetate (^{99m}Tc)); QV09EA02 (technetium technegas (^{99m}Tc)); QV09EA03 (technetium nanocolloid (^{99m}Tc)); QV09EB01 (technetium macrosalb (^{99m}Tc)); QV09EB02 (technetium microspheres (^{99m}Tc)); QV09FX01 (technetium pertechnetate (^{99m}Tc)); QV09GA01 (technetium sestamibi (^{99m}Tc)); QV09GA02 (technetium tetrofosmin (^{99m}Tc)); QV09GA03 (technetium teboroxime (^{99m}Tc)); QV09GA04 (technetium human albumin (^{99m}Tc)); QV09GA05 (technetium furifosmin (^{99m}Tc)); QV09GA06 (technetium stannous agent labelled cells (^{99m}Tc)); QV09GA07 (technetium apcitide (^{99m}Tc)); QV09HA01 (technetium human immunoglobulin (^{99m}Tc)); QV09HA02 (technetium exametazime labelled cells (^{99m}Tc)); QV09HA03 (technetium antigranulocyte antibody (^{99m}Tc)); QV09HA04 (technetium sulesomab (^{99m}Tc)); QV09IA01 (technetium antiCEA antibody (^{99m}Tc)); QV09IA02 (technetium antimelanoma antibody (^{99m}Tc)); QV09IA03 (technetium pentavalent succimer (^{99m}Tc)); QV09IA04 (technetium votumumab (^{99m}Tc)); QV09IA05 (technetium depreotide (^{99m}Tc)); QV09IA06 (technetium arcitumomab (^{99m}Tc)); QV09IA07 (technetium hynic-octreotide (^{99m}Tc)).
UNII — Z8E46IA45W (technetium (^{99m}Tc) albumin aggregated); IV7T84QA4T (technetium (^{99m}Tc) apcitide); H25WJA31XE (technetium (^{99m}Tc) bicisate); 9M48M2SF02 (technetium (^{99m}Tc) depreotide); QTJ2VIW97T (technetium (^{99m}Tc) disofenin); 13W7DMI45X (technetium (^{99m}Tc) etidronate); 3B744AG22N (technetium (^{99m}Tc) exametazime); I853LE095B (technetium (^{99m}Tc) gluceptate); 36ITO9SKQJ (technetium (^{99m}Tc) mertiatide); F2NQ468L52 (technetium (^{99m}Tc) mebrofenin); X89XV46R07 (technetium (^{99m}Tc) medronate); 36ITO9SKQJ (technetium (^{99m}Tc) mertiatide); UQ9G2F6BHI (technetium (^{99m}Tc) nitridocade); MG4KI49HHJ (technetium (^{99m}Tc) oxidronate); VW78417PU1 (technetium (^{99m}Tc) pentetate); 971Z4W1S09 (technetium (^{99m}Tc) sestamibi); A0730CX801 (technetium (^{99m}Tc) sodium pertechnetate); 494JNQ8L28 (technetium (^{99m}Tc) succimer); 556Q0P6PB7 (technetium (^{99m}Tc) sulfur colloid); UT0WHJ4951 (technetium (^{99m}Tc) teboroxime); 42FOP1YX93 (technetium (^{99m}Tc) tetrofosmin).

NOTE. Macrosalb (^{99m}Tc) is *rINN* and *BAN*.
Technetium Tc 99m Albumin Aggregated, Technetium Tc 99m Albumin Colloid, and Technetium Tc 99m Albumin Microaggregated are *USAN*.
Technetium Tc 99m Antimony Trisulfide Colloid is *USAN*.
Technetium (^{99m}Tc) Apcitide is *rINN* and Technetium Tc 99m Apcitide is *USAN*.
Technetium (^{99m}Tc) Bicisate is *rINN*, Technetium[^{99m}Tc] Bicisate is *BAN*, and Technetium Tc 99m Bicisate is *USAN*.
Technetium (^{99m}Tc) Depreotide is *rINNM*.
Technetium (^{99m}Tc) Etarfolatide is *pINN* and Technetium Tc 99m Etarfolatide is *USAN*.
Technetium Tc 99m Exametazime is *USAN*.
Technetium (^{99m}Tc) Fanolesomab is *rINN* and Technetium Tc 99m Fanolesomab is *USAN*.
Technetium (^{99m}Tc) Furifosmin is *rINN* and Technetium Tc 99m Furifosmin is *USAN*.
Technetium Tc 99m Lidofenin is *USAN*.
Technetium Tc 99m Mebrofenin is *USAN*.
Technetium Tc 99m Medronate Disodium is *USAN*.
Technetium Tc 99m Mertiatide is *USAN*.
Technetium (^{99m}Tc) Nitridocade is *rINN* and Technetium Tc 99m is Nitridocade is *USAN*.
Technetium (^{99m}Tc) Nofetumomab Merpentan is *rINN*.
Technetium Tc 99m Pentetate Calcium Trisodium is *USAN*.
Technetium (^{99m}Tc) Pintumomab is *rINN*.
Technetium Tc 99m Red Blood Cells is *USAN*.
Technetium (^{99m}Tc) Sestamibi is *rINN*, Technetium[^{99m}Tc] Sestamibi is *BAN*, and Technetium Tc 99m Sestamibi is *USAN*.
Technetium (^{99m}Tc) Siboroxime is *rINN* and Technetium Tc 99m Siboroxime is *USAN*.
Technetium Tc 99m Sulfur Colloid is *USAN*.
Technetium (^{99m}Tc) Teboroxime is *rINN*, Technetium[^{99m}Tc] Teboroxime is *BAN*, and Technetium Tc 99m Teboroxime is *USAN*.
Technetium[^{99m}Tc] Tiatide is *BAN*.
Technetium Tc 99m Tilmanocept is *USAN*.
HALF-LIFE. 6.01 hours.

Uses and Administration

Technetium-99m (^{99m}Tc) decays by isomeric transition and emits gamma rays (see Radioactive Decay, p. 2222.1). It is a daughter of molybdenum-99 (^{99}Mo, half-life 65.9 hours) and because of its short half-life is normally prepared just before use by elution from a sterile generator consisting of molybdenum-99 adsorbed onto alumina in a glass column. Technetium-99m as pertechnetate ($^{99m}TcO_4^-$) is obtained by elution with a sterile solution of sodium chloride 0.9%. Radiopharmaceuticals of technetium-99m are prepared shortly after elution to reduce loss by decay.

Because it has a short half-life and can be given in relatively large doses, and because the energy of its gamma-emission is readily detected, technetium-99m is very widely used, either as the pertechnetate or in the form of various labelled compounds, particles, and colloids for scanning bone and organs such as the brain, heart, kidney, liver, lung, spleen, and thyroid.

Sodium pertechnetate (^{99m}Tc) is used orally or intravenously for angiography and for imaging blood pools, brain, salivary glands, and the thyroid gland. Topical application to the eye is used for studying nasolachrymal drainage and the intraurethral route for imaging the urinary tract. Potassium perchlorate may be given before the pertechnetate to prevent uptake in the thyroid or choroid plexus.

Macroaggregates of human albumin labelled with technetium-99m (macrosalb (^{99m}Tc)) are used in lung scanning for the detection of abnormal lung perfusion patterns. Labelled macroaggregates of albumin have also been used in venography for the detection of deep-vein thrombosis of the legs. Technetium (^{99m}Tc) apcitide is a labelled peptide that binds to the glycoprotein IIb/IIIa receptor of activated platelets, and is also used for imaging of deep-vein thrombosis.

When technetium-99m bound to human serum albumin is given intravenously it becomes evenly distributed in the circulation and highly vascular organs or pools of blood may be readily located. Such a preparation is used in the examination of the heart.

Technetium-99m in the form of a colloid, such as albumin, sulfur, antimony sulfide, calcium phytate, or tin, is used intravenously for the examination of the liver, spleen, and bone marrow. Sulfur colloid (^{99m}Tc) may be given orally

for oesophageal and gastrointestinal imaging, and subcutaneously for scanning of the lymphatic system. Colloidal rhenium sulfide (^{99m}Tc) has been used for sentinel lymph node detection in patients with malignancies.

Technetium-99m complexes of iminodiacetic acid derivatives, such as disofenin, etifenin, lidofenin, and mebrofenin are used intravenously in the investigation of hepatic function and in the imaging of the hepatobiliary system.

Agents used intravenously in both brain and renal imaging are technetium-99m-labelled gluceptate and pentetate. Technetium (^{99m}Tc) gluconate and technetium (^{99m}Tc) glucoheptonate were used for renal studies; they are used for labelling red blood cells. Other technetium-99m-labelled compounds are used in brain or kidney scanning; for instance, labelled bicisate and exametazime have been used in brain imaging and betiatide, mertiatide, and succimer have been used in kidney studies. The pentetate is also given by inhalation for lung ventilation imaging.

For bone scanning various labelled phosphate compounds may be used and include medronate, oxidronate, and pyrophosphate, all given intravenously. Technetium-99m as the pyrophosphate was also used in cardiac scintigraphy; it is also used to label red blood cells for use in blood pool scintigraphy and for the detection of gastrointestinal bleeding.

Compounds used intravenously in cardiac imaging include technetium-99m-labelled sestamibi, teboroxime, and tetrofosmin. Technetium (^{99m}Tc) sestamibi is also used for breast imaging.

Technetium-99m-labelled leucocytes (prepared using exametazime) are used for localisation of sites of inflammation or infection. Red blood cells are labelled with technetium-99m and used for blood pool imaging, and detection of gastrointestinal bleeding.

Monoclonal antibodies labelled with technetium-99m, such as arcitumomab and nofetumomab merpentan, are used for the detection and localisation of malignant neoplasms. Labelled sulesomab is used in the detection of osteomyelitis. Labelled fanolesomab was used in the diagnosis of appendicitis but was withdrawn from the market due to severe adverse effects. Technetium (^{99m}Tc) depreotide is a labelled peptide used intravenously for imaging of pulmonary malignancy.

Many other technetium-99m-labelled compounds have been prepared and used in different clinical studies for the examination of different organs or systems. Use with other radionuclides includes subtraction scanning with thallium-201 to detect parathyroid tumours.

Reviews.

1. Banerjee S, *et al.* Evolution of Tc-99m in diagnostic radiopharmaceuticals. *Semin Nucl Med* 2001; 31: 260–77.
2. Mease RC, Lambert C. Newer methods of labeling diagnostic agents with Tc-99m. *Semin Nucl Med* 2001; 31: 278–85.
3. Arano Y. Recent advances in 99mTc radiopharmaceuticals. *Ann Nucl Med* 2002; 16: 79–93.
4. Decristoforo C, Mather SJ. The influence of chelator on the pharmacokinetics of 99mTc-labelled peptides. *Q J Nucl Med* 2002; 46: 195–205.
5. Ballinger JR. The influence of carrier on 99mTc radiopharmaceuticals. *Q J Nucl Med* 2002; 46: 224–32.
6. Eckelman WC. Unparalleled contribution of technetium-99m to medicine over 5 decades. *JACC Cardiovasc Imaging* 2009; 2: 364–8.

Adverse Effects and Precautions

Hypersensitivity reactions have been reported with technetium-99m preparations.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to technetium-99m since radioactivity has been reported to be present in breast milk for 15 to 72 hours.

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 01/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Cardiolite; Ceretec; Myoview; Neurolite; *Austria*: TechneScan MAG3; Ultra Technekow FM; *Belg.*: Amerscan Medronate†; Maasol†; Myoview†; Nanocoll†; Stabilised Ceretec†; TechneScan DMSA; TechneScan DTPA; TechneScan HDP; TechneScan PYP; Ultra TechneKow FM; Venticoll†; *Cz.*: 6-MDP, 8-MDP; Amerscan Hepatate†; Amerscan Medronate; Amerscan Stannous†; Brain-Spect; Cardio-Spect; Cardiolite†; Ceretec; Drytec; DTPA; Elumatic III; Hibida; HM-PAO Kit†; Leuco-Scint; LeukoScan; Macro-Albumon; Macrotec; Mag 3; Myoview; Nano-Albumon; Nanocis; Nanocoll; NeoSpect†; Neurolite; Neuroscan; Pulmocis; Scintimun; Senti-Scint; Stamicis; TechneScan DMSA; TechneScan DTPA; TechneScan Has†; TechneScan HDP; TechneScan HIG; TechneScan LyoMAA; TechneScan MAG3; TechneScan PYP; TechneScan Sestamibi; Trimetyl-HIDA; Ultra Technekow FM; UltraTag RBC; *Denm.*: Drytec; Neurolite; Pulmotec; *Fin.*: Amerscan Hepatate†; Amerscan Medronate†; Amerscan Stannous; Angiocis; Bridatec; Cardiolite; Ceretec; Drytec; Maasol; Myoview; Nanocoll; Neurolite; Osteocis; Osteosol†; Pentacis; Pulmocis; Pulmotec; Renocis; Sammibi; Stamicis; Teceos; TechneScan LyoMAA; TechneScan Sestamibi; Vasculocis; Venticoll; *Fr.*: Amerscan Etain Stanneux†; Amerscan Hepatate†; Amerscan Medronate†; Amerscan Pentetate†; Angiocis; Cardiolite; Cerestab; Ceretec; Elumatic; Myoview; Nanocoll; NeoSpect†; Neurolite; Osteocis; Pentacis; Phytacis; Pulmocis; Pulmotec; Renocis; Scintimun; Stamicis; Teceos; TechneScan DMSA; TechneScan HDP; TechneScan LyoMAA; Vasculocis; *Ger.*: Draxmibi†; Macrosalb Draximage; *Gr.*: Humaspect†; *Irl.*: Amerscan Medronate; Amerscan Stannous†; Ceretec; Choledam; Drytec; Elumatic; LeukoScan; Myoview; NeoSpect†; Osteocis; Pentacis; Pulmocis; Pulmotec; Renocis; Scintimun; Stamicis; TechneScan DMSA; TechneScan DTPA; TechneScan HDP; TechneScan LyoMAA; TechneScan MAG3; TechneScan MIBI; TechneScan PYP; Ultra TechneKow FM; *Israel*: Ceretec; Myoview; Neurolite; RBC-Kit; Technelite†; *Ital.*: Cardiolite; Ceretec; LeukoScan; Myoview; NeoSpect†; Neurolite; TechneScan MAG3; *Neth.*: Amerscan Hepatate†; Amerscan Stannous†; Bridatec; Cardiolite; Ceretec; Choledam†; DraxMibi; Drytec; Elumatic; Hepatate; LeukoScan; Maasol; Macrosalb Draximage†; Macrosalbt†; Medronaat Draximage; Myoview; Nanocoll; NeoSpect†; Neurolite†; Osteocis; Penetaat Draximage†; Phytacis; Pulmocis; Pulmotec; Scintimun; Stamicis; Stannous Agent; Teceos; TechneScan DMSA; TechneScan DTPA; TechneScan HDP; TechneScan LyoMAA; TechneScan MAG3; TechneScan PYP; TechneScan Sestamibi; Tekcis; Ultra TechneKow; UltraTag; *Pol.*: LeukoScan; Scintimun; *Port.*: Angiocis; Bridatec†; Cardiolite†; Ceretec; Elumatic; LeukoScan; Macrotec; Mertioscan; Myoview; Nanocis; Nanocoll; NeoSpect†; Neurolite; Osteocis; Pentacis; Phytacis; Pulmotec; Renocis; Scintimun; Stamicis; TechneScan DTPA; TechneScan HDP; TechneScan MAG3; TechneScan Sestamibi; Ultra TechneKow FM; *Rus.*: Myoview (Миовью); NeoSpect (Неоспект); *Spain*: Angiocis; Bridatec; Cardiolite; Ceretec; Drytec; Elumatic; LeukoScan; Macrotec; Myoview; Nanocoll; NeoSpect†; Neurolite†; Osteocis; Pentacis; Pulmotec; Scintimun; Stamicis; TechneScan DTPA; TechneScan HDP; TechneScan LyoMAA; TechneScan MAG3; Ultra Technekow; *Switz.*: Maasol; Myoview; Nanocoll; Teceos; TechneScan HDP; Tekcis; UltratechneKow; *UK*: Amerscan DMSA; Amerscan Hepatate; Amerscan Medronate; Amerscan Pentetate; Amerscan Pulmonate; Amerscan Stannous; Amertec; Angiocis; Cardiolite; CEA-Scan; Ceretec; Choledis; Drytec; Myoview; Nanocoll; Osteocis; Pentacis; Pulmocis; Renocis; *USA*: AcuTect; Cardiolite; CEA-Scan; Choletec; Lymphoseek; Miraluma; NeoTect; TechneScan HDP.

Multi-ingredient Preparations. *Fin.*: Tekcis; *Spain*: Teceos.

Pharmacopoeial Preparations

Ph. Eur.: Sodium Pertechnetate(^{99m}Tc) Injection (Fission); Sodium Pertechnetate(^{99m}Tc) Injection (Non-fission); Technetium (^{99m}Tc) Mebrofenin Injection; Technetium(^{99m}Tc) Bicisate Injection; Technetium(^{99m}Tc) Colloidal Rhenium Sulphide Injection; Technetium(^{99m}Tc) Colloidal Sulphur Injection; Technetium(^{99m}Tc) Colloidal Tin Injection; Technetium(^{99m}Tc) Etifenin Injection; Technetium(^{99m}Tc) Exametazime Injection; Technetium(^{99m}Tc) Gluconate Injection; Technetium(^{99m}Tc) Human Albumin Injection; Technetium(^{99m}Tc) Macrosalb Injection; Technetium(^{99m}Tc) Medronate Injection; Technetium (^{99m}Tc) Mertiatide Injection; Technetium(^{99m}Tc) Microspheres Injection; Technetium(^{99m}Tc) Pentetate Injection; Technetium (^{99m}Tc) Sestamibi Injection; Technetium(^{99m}Tc) Succimer Injection; Technetium(^{99m}Tc) Tin Pyrophosphate Injection;

USP 36: Sodium Pertechnetate Tc 99m Injection; Technetium ^{99m}Tc Fanolesomab Injection; Technetium Tc 99m (Pyro- and trimeta-) Phosphates Injection; Technetium Tc 99m Albumin Aggregated Injection; Technetium Tc 99m Albumin Colloid Injection; Technetium Tc 99m Albumin Injection; Technetium Tc 99m Apcitide Injection; Technetium Tc 99m Arcitumomab Injection; Technetium Tc 99m Bicisate Injection; Technetium Tc 99m Depreotide Injection; Technetium Tc 99m Disofenin Injection; Technetium Tc 99m Etidronate Injection; Technetium Tc 99m Exametazime Injection; Technetium Tc 99m Gluceptate Injection; Technetium Tc 99m Lidofenin Injection; Technetium Tc 99m Mebrofenin Injection; Technetium Tc 99m Medronate Injection; Technetium Tc 99m Mertiatide Injection; Technetium Tc 99m Nofetumomab Merpentan Injection; Technetium Tc 99m Oxidronate Injection; Technetium Tc 99m Pentetate Injection; Technetium Tc 99m Pyrophosphate Injection; Technetium Tc 99m Red Blood Cells Injection; Technetium Tc 99m Sestamibi Injection; Technetium Tc 99m Succimer Injection; Technetium Tc 99m Sulfur Colloid Injection; Technetium Tc 99m Tetrofosmin Injection.

Thallium-201

Tal-201; Talio 201; Tálio-201; Tallio-201; Tallium-201; Таллий-201; Pallín-201.

CAS — 15064-65-0 (thallium-201); 55172-29-7 (thallous (^{201}Tl) chloride).

ATC — V09GX01 (thallium chloride ($_{201}$Tl)).

ATC Vet — QV09GX01 (thallium chloride ($_{201}$Tl)).

UNII — H91Z8HBK18 (thallium-201).

NOTE. Thallous Chloride Tl 201 is *USAN*.

HALF-LIFE. 72.9 hours.

Profile

Thallium-201 (^{201}Tl) is a radioactive isotope of thallium that decays by electron capture and emits X-rays and gamma rays (see Radioactive Decay, p. 2222.1). It is given intravenously in the form of thallous chloride (^{201}Tl) for scanning the myocardium in the investigation of acute myocardial infarction. It is also used with exercise stress testing as an adjunct in the diagnosis of ischaemic heart disease. Adenosine (see Ischaemic Heart Disease, p. 1291.2), dipyridamole (see Myocardial Imaging, p. 1362.3), or dobutamine (see Diagnosis and Testing, p. 1366.2) may be used to induce pharmacological stress in those patients unable to tolerate exercise.

A dual isotope method has been developed to aid the diagnosis of coronary artery disease, using thallous chloride (^{201}Tl) and technetium-99m-labelled sestamibi.

Other uses include localisation of sites of parathyroid hyperactivity and tumour imaging.

References.

1. Steien S, Aaseth J. Thallium-201 as an agent for myocardial imaging studies. *Analyst* 1995; 120: 779–81.
2. Sumiya H, *et al.* Nuclear imaging of bone tumors: thallium-201 scintigraphy. *Semin Musculoskelet Radiol* 2001; 5: 177–82.
3. Berk P, *et al.* Thallium-201 imaging in the assessment of tumor response to anti-tumor treatments. *Q J Nucl Med* 2003; 47: 63–74.
4. Okudan B, Smitherman TC. The value and throughput of rest Thallium-201/stress Technetium -99m sestamibi dual-isotope myocardial SPECT. *Anadolu Kardiyol Derg* 2004; 4: 161–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: DRN 8103.

Pharmacopoeial Preparations

Ph. Eur.: Thallous(^{201}Tl) Chloride Injection;

USP 36: Thallous Chloride Tl 201 Injection.

Tritium

Hidrogeno 3; Hydrogen-3; Tricium; Tritio; Tritio; Trizio; Тритий.

CAS — 10028-17-8.

NOTE. Water, Tritiated is *USAN*.

HALF-LIFE. 12.3 years.

Profile

Tritium is a radioactive isotope of hydrogen that emits beta particles (see Radioactive Decay, p. 2222.1). It has been used in the form of tritiated water to determine the total body water by a dilution technique.

Preparations

Pharmacopoeial Preparations

Ph. Eur.: Tritiated(^{3}H) Water Injection.

Xenon-127

Ksenon-127; Xenón 127; Xénon-127; Xenonum-127; Ксенон-127.

CAS — 13994-19-9.

ATC — V09EX02 (xenon gas ($_{127}$Xe)).

ATC Vet — QV09EX02 (xenon gas ($_{127}$Xe)).

UNII — H95KBR1GD8.

HALF-LIFE. 36.4 days.

Profile

Xenon-127 (^{127}Xe) is a radioactive isotope of xenon (p. 1917.3) that emits gamma radiation (see Radioactive Decay, p. 2222.1). It was used by inhalation for pulmonary function studies and lung imaging.

Preparations

Pharmacopoeial Preparations

USP 36: Xenon Xe 127.

Xenon-133

Ksenon-133; Xenón 133; Xénon (^{133}Xe); Xenon (^{133}Xe) (INN); Xenón (^{133}Xe); Xenon Xe 133 (USAN); Xenonum (^{133}Xe); Ксенон-(^{133}Xe).

CAS — 14932-42-4.

ATC — V09EX03 (xenon gas ($_{133}$Xe)).

ATC Vet — QV09EX03 (xenon gas ($_{133}$Xe)).

UNII — X3P9A5HNYF.

HALF-LIFE. 5.24 days.

Profile

Xenon-133 (^{133}Xe) is a radioactive isotope of xenon (p. 1917.3) that emits beta and gamma radiation (see

The symbol † denotes a preparation no longer actively marketed

Radioactive Decay, p. 2222.1). In the gaseous form, it is mixed with air or oxygen in a bag or in a closed respirator system or spirometer. When the gas is stopped, xenon-133 is excreted promptly and completely through the lungs. It is used by inhalation in pulmonary function studies and lung imaging. It has also been used in cerebral blood flow studies.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Xenon(^{133}Xe) Injection;
USP 36: Xenon Xe 133 Injection; Xenon Xe 133.

Yttrium-90

Itr-90; Itrio 90; Itrio-90; Ittrio-90; Ittrium-90; Yttri-90; Иттрий-90.

CAS — 10098-91-6 (yttrium-90); 943976-23-6 (yttrium (^{90}Y) clivatuzumab tetraxetan); 501423-23-0 (yttrium (^{90}Y) epratuzumab); 501423-25-2 (yttrium (^{90}Y) epratuzumab tetraxetan); 501423-27-4 (yttrium (^{90}Y) labetuzumab); 501423-30-9 (yttrium (^{90}Y) labetuzumab tetraxetan); 500784-58-7 (yttrium (^{90}Y) tacatuzumab); 476413-07-7 (yttrium (^{90}Y) tacatuzumab tetraxetan).

ATC — V10AA01 (yttrium citrate colloid ($_{90}$Y)); V10AA02 (yttrium ferrihydroxide colloid ($_{90}$Y)); V10AA03 (yttrium silicate colloid ($_{90}$Y)); V10XX02 (ibritumomab tiuxetan ($_{90}$Y)).

ATC Vet — QV10AA01 (yttrium citrate colloid ($_{90}$Y)); QV10AA02 (yttrium ferrihydroxide colloid ($_{90}$Y)); QV10AA03 (yttrium silicate colloid ($_{90}$Y)); QV10XX02 (ibritumomab tiuxetan ($_{90}$Y)).

UNII — 1K8M7UR6O1 (yttrium-90); 433ME2ATHW (yttrium-90 ion); 2L271110ED (yttrium clivatuzumab tetraxetan (^{90}Y)); J36232195E (yttrium epratuzumab tetraxetan (^{90}Y)); QA846JAV5B (yttrium ibritumomab tiuxetan (^{90}Y)); GJ2416WK6Y (yttrium tacatuzumab tetraxetan (^{90}Y)).

NOTE. Yttrium (^{90}Y) Clivatuzumab Tetraxetan is *rINN* and Yttrium Y 90 Clivatuzumab Tetraxetan is *USAN*.
Yttrium Y 90 Epratuzumab is *USAN*.
Yttrium Y 90 Epratuzumab Tetraxetan is *USAN*.
Yttrium Y 90 Labetuzumab is *USAN*.
Yttrium Y 90 Labetuzumab Tetraxetan is *USAN*.
Yttrium Y 90 Tacatuzumab is *USAN*.
Yttrium (^{90}Y) Tacatuzumab Tetraxetan is *rINN* and *BAN* and Yttrium Y 90 Tacatuzumab Tetraxetan is *USAN*.
HALF-LIFE. 64.1 hours.

Profile

Yttrium-90 (^{90}Y) is a radioactive isotope of yttrium that decays by beta emission (see Radioactive Decay, p. 2222.1). It is the daughter nuclide of strontium-90 (^{90}Sr). Yttrium (^{90}Y) chloride conjugated to ibritumomab tiuxetan (p. 804.3) is used in the treatment of non-Hodgkin's lymphoma (p. 696.3). Conjugates with various other monoclonal antibodies and compounds are also under investigation for malignant neoplasms.

Yttrium-90, in the form of a colloidal suspension of yttrium silicate (^{90}Y) has been used for instillation into pleural or peritoneal cavities in the treatment of malignant pleural effusion or malignant ascites.

Yttrium-90, as either yttrium citrate (^{90}Y) or yttrium silicate (^{90}Y), has also been used in the treatment of arthritic conditions of the knee joint.

Yttrium-90 enclosed in glass or resin microspheres has been used for the local treatment of malignant neoplasms of the liver.

References.

1. Heuft-Dorenbosch LL, *et al.* Yttrium radiosynoviorthesis in the treatment of knee arthritis in rheumatoid arthritis: a systematic review. *Ann Rheum Dis* 2000; **59**: 583–6.
2. Gordon LI. Practical considerations and radiation safety in radioimmunotherapy with yttrium 90 ibritumomab tiuxetan (Zevalin). *Semin Oncol* 2003; **30** (6 suppl 17): 23–8.
3. Cheson BD. The role of radioimmunotherapy with yttrium-90 ibritumomab tiuxetan in the treatment of non-Hodgkin lymphoma. *BioDrugs* 2005; **19**: 309–22.
4. Cheung MC, *et al.* Members of the Hematology Disease Site Group of the Cancer Care Ontario Program in Evidence-Based Care. Yttrium 90 ibritumomab tiuxetan in lymphoma. *Leuk Lymphoma* 2006; **47**: 967–77. Correction. *ibid.*; 1719–20.
5. Salem R, Hunter RD. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma: a review. *Int J Radiat Oncol Biol Phys* 2006; **66** (suppl): S83–S88.
6. Kampen WU, *et al.* Therapeutic status of radiosynoviorthesis of the knee with yttrium [^{90}Y] colloid in rheumatoid arthritis and related indications. *Rheumatology (Oxford)* 2007; **46**: 16–24.
7. Gisselbrecht C, *et al.* Current status and future perspectives for yttrium-90 (^{90}Y)-ibritumomab tiuxetan in stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2007; **40**: 1007–17.
8. Zinzani PL, *et al.* Consensus conference: implementing treatment recommendations on yttrium-90 immunotherapy in clinical practice—report of a European workshop. *Eur J Cancer* 2008; **44**: 366–73.
9. Khodjibekova M, *et al.* Selective internal radiation therapy with Yttrium-90 for unresectable liver tumours. *Rev Recent Clin Trials* 2007; **2**: 212–16.
10. van der Zant FM, *et al.* Radiation synovectomy with (90)Yttrium, (186) Rhenium and (169)Erbium: a systematic literature review with meta-analyses. *Clin Exp Rheumatol* 2009; **27**: 130–9.
11. Riaz A, *et al.* Yttrium-90 radioembolization using TheraSphere in the management of primary and secondary liver tumors. *Q J Nucl Med Mol Imaging* 2009; **53**: 311–16.
12. Van De Wiele C, *et al.* Yttrium-90 labelled resin microspheres for treatment of primary and secondary malignant liver tumors. *Q J Nucl Med Mol Imaging* 2009; **53**: 317–24.
13. Riaz A, *et al.* Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. *J Vasc Interv Radiol* 2009; **20**: 1121–30.
14. Kennedy AS, Salem R. Radioembolization (yttrium-90 microspheres) for primary and metastatic hepatic malignancies. *Cancer J* 2010; **16**: 163–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Ytracis; Ytriga; *Fr.*: Ytracis; *Hung.*: Ytracis; *Irl.*: Ytracis; Yttriga; *Israel*: Ytracis; *Ital.*: Ytracis; *Neth.*: Ytracis; Yttriga; *Pol.*: Ytracis; Yttriga; *Port.*: Ytracis; Yttriga; *Spain*: Ytracis; Ytriga; *Switz.*: Ytracis; *UK*: Ytracis.

Pharmacopoeial Preparations
USP 36: Yttrium Y 90 Ibritumomab Tiuxetan Injection.

Zirconium-89

Cyrkon-89; Sirkon-89; Tsirkoonium-89; Zircônio-89; Zirconio-89; Zirconio-89; Zirconiu; Zirkónium-89; Zirkonium-89; Цирконий-89.

CAS — 13981-27-6.

HALF-LIFE. 78 hours.

Profile

Zirconium-89 (^{89}Zr) is a radioactive isotope of zirconium (p. 2650.3) that emits positrons and gamma rays and decays by electron capture. It is used in positron-emission tomography (PET; see Radioactive Decay, p. 2222.1) to confirm and quantify tumour uptake of monoclonal antibodies ('immuno-PET').

References.

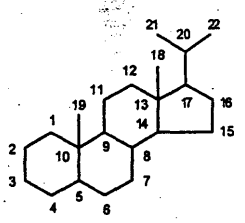
1. Perk LR, *et al.* *p*-Isothiocyanatobenzyl-desferrioxamine: a new bifunctional chelate for facile radiolabeling of monoclonal antibodies with zirconium-89 for immuno-PET imaging. *Eur J Nucl Med Mol Imaging* 2010; **37**: 250–9.
2. Vosjan MJ, *et al.* Conjugation and radiolabeling of monoclonal antibodies with zirconium-89 for PET imaging using the bifunctional chelate p-isothiocyanatobenzyl-desferrioxamine. *Nat Protoc* 2010; **5**: 739–43.
3. Dijkers EC, *et al.* Biodistribution of ^{89}Zr-trastuzumab and PET imaging of HER2-positive lesions in patients with metastatic breast cancer. *Clin Pharmacol Ther* 2010; **87**: 586–92.
4. van Dongen GAMS, Vosjan MJWD. Immuno-positron emission tomography: shedding light on clinical antibody therapy. *Cancer Biother Radiopharm* 2010; **25**: 375–85.

Sex Hormones and their Modulators

The male and female sex organs, the adrenal cortex, and the placenta produce steroidal hormones that influence the development and maintenance of structures directly and indirectly associated with reproduction. The secretion of these sex hormones is controlled by gonadotrophic hormones of the anterior lobe of the pituitary gland (and in pregnancy, from the placenta); the secretion of pituitary gonadotrophic hormones is in turn influenced by the hypothalamus and also by the concentration of circulating sex hormones. There are 3 groups of endogenous sex hormones, androgens, oestrogens, and progestogens, all of which are derived from the same steroidal precursors. The progestogenic hormone, progesterone, is formed from pregnenolone, and both of these compounds may be converted to androgen precursors such as androstenedione. Androstenedione is converted to the androgenic hormone testosterone by hydroxysteroid dehydrogenases. Oestrogenic hormones are synthesised from androstenedione (and also from testosterone) by the action of aromatase.

Figure 1 (below) shows the basic steroidal skeleton structure.

Figure 1. Steroidal skeleton.



Testosterone is the main androgenic hormone formed in the interstitial (*Leydig*) cells of the testes. A small proportion of circulating testosterone is also derived from the metabolism of less potent androgens secreted by the adrenal cortex and ovaries. In many target tissues testosterone is then converted to the more active dihydrotestosterone by 5α-reductase. Some testosterone also undergoes peripheral conversion to oestradiol.

Testosterone controls the development and maintenance of the male sex organs and the male secondary sex characteristics. It also produces systemic anabolic effects, such as increased retention of nitrogen, calcium, sodium, potassium, chloride, and phosphate. This leads to an increase in water retention and bone growth. The skin becomes more vascular and less fatty and erythropoiesis is increased.

Numerous derivatives of testosterone have been developed. Alkylation at the 17α position results in derivatives that are orally active, but associated with a risk of hepatotoxicity (see Table 1, below). Esterification of the 17β-hydroxyl group increases lipid solubility and is used to prepare long-acting intramuscular preparations (e.g. testosterone enantate). Removal of the 19-methyl group is reported to improve the anabolic to androgenic ratio (e.g. nandrolone). The derivatives also vary in their plasma protein binding affinity, and degree of conversion to dihydrotestosterone and aromatic conversion to oestrogen. Numerous other structural modifications have been made.

Oestradiol is the most active of the naturally occurring oestrogens formed from androgen precursors in the ovarian follicles of premenopausal women. In men and postmenopausal women (and to an insignificant extent in premenopausal women) oestrogens are also formed in adipose tissue from adrenal androgens.

Oestrogens control the development and maintenance of the female sex organs, secondary sex characteristics, and mammary glands as well as certain functions of the uterus and its accessory organs (particularly the proliferation of the endometrium, the development of the decidua, and the cyclic changes in the cervix and vagina). Large amounts of oestradiol are also formed in the placenta; in late pregnancy, this increases the spontaneous activity of the uterine muscle and its response to oxytocic drugs. The additional activity of progesterone is essential for the complete biological function of the female sex organs. Oestrogens also have some direct effects on metabolic processes, including those affecting bone mass, lipids, carbohydrates, and proteins.

Table 1. 17α-Alkylated testosterone derivatives

Danazol	Norethandrolone
Ethylestrenol	Oxandrolone
Fluoxymesterone	Oxymetholone
Methandienone	Stanozolol
Methyltestosterone	

Many oestrogens are used therapeutically. Ethinyl substitution at the C17 position has led to the development of synthetic oestrogens such as ethinylestradiol and mestranol, which have greatly improved potency and oral activity. Oral activity of natural oestrogens is improved by esterification (e.g. estradiol valerate) or by conjugation (e.g. estrone sulfate). Esterification also increases solubility in lipid vehicles and is used to prepare long-acting intramuscular preparations.

Several nonsteroidal oestrogens, including chlorotrianisene, dienestrol, and diethylstilbestrol, have also been used.

Progesterone is the main hormone secreted by the corpus luteum. It acts on the endometrium by converting the proliferative phase induced by oestrogen to a secretory phase thereby preparing the uterus to receive the fertilised ovum. Progesterone has a catabolic action and causes a slight rise in basal body temperature during the secretory phase of menstruation. During pregnancy the placenta produces large quantities of progesterone, which suppresses uterine motility and is responsible for the further development of the breasts.

Progestogens (gestagens, progestagens, progestins) are synthetic compounds with actions similar to those of progesterone. They are either progesterone derivatives or 19-nortestosterone analogues. The 19-nortestosterone analogues (such as norethisterone and norgestrel) possess some androgenic activity, but some newer norgestrel derivatives (desogestrel, gestodene, and norgestimate) have little androgenic activity. The progesterone derivatives dydrogesterone, hydroxyprogesterone, and medroxyprogesterone are less androgenic than the 19-nortestosterone analogues. The progesterone derivatives chlormadinone, and particularly cyproterone, have anti-androgenic activity.

The principal natural and synthetic sex hormones covered in this chapter are thus:

- **androgens and anabolic steroids**, typified by testosterone (p. 2305.1)
- **oestrogens**, typified by estradiol (p. 2271.1)
- **progestogens**, typified by progesterone (p. 2300.2)

Other related substances also described in this chapter are:

- drugs with mainly **weak androgenic** properties such as danazol and gestrinone
- drugs that combine **oestrogenic and progestogenic** properties such as tibolone
- drugs with mainly **anti-androgenic** properties including the progesterone derivative cyproterone acetate. Those anti-androgens used principally in the hormonal treatment of prostate cancer are covered in the Antineoplastics chapter; they include the nonsteroidal drugs bicalutamide (p. 749.1), flutamide (p. 798.2), and nilutamide (p. 836.2). The nonsteroidal 5α-reductase inhibitors finasteride (p. 2358.3) and dutasteride (p. 2357.2) and the plant extract saw palmetto (p. 2363.3), used in the treatment of benign prostatic hyperplasia, are covered in the Urological Drugs chapter
- drugs with mainly **anti-oestrogenic** properties. These include the nonsteroidal anti-oestrogens clomifene and cyclofenil. Those anti-oestrogens used principally in the hormonal treatment of breast cancer are covered in the Antineoplastics chapter; they include the oestrogen receptor antagonists tamoxifen (p. 860.2) and toremifene (p. 873.3), and various aromatase inhibitors such as formestane (p. 799.2) and anastrozole (p. 742.1)
- **selective oestrogen receptor modulators**, such as ormeloxifene and raloxifene, that have agonist and antagonist effects in different tissues
- **gonad-regulating hormones** (see p. 2251.2 for more detail) include endogenous and recombinant forms of luteinising and follicle-stimulating hormones, and their releasing hormone gonadorelin and its analogues.

The therapeutic applications of sex hormones and related substances are broad and cover many circumstances where hormonal manipulation is desirable. Major applications are the use of oestrogens and progestogens for **contraception** (p. 2232.3) and for the alleviation of **menopausal symptoms** (p. 2245.1). A physiological application is the use of sex hormones or gonad-regulating hormones in the management of **delayed puberty** (p. 2252.1) and **hypogonadism** (p. 2252.3). Other clinical applications include the management of **benign prostatic hyperplasia** (p. 2347.1), **endometriosis** (p. 2264.1), **gynaecomastia** (p. 2264.3), **hirsutism** (p. 2262.1), **infertility** (p. 2253.1), **mastalgia** (p. 2265.1), **menorrhagia** (p. 2300.3), and **premenstrual syndrome** (p. 2272.3). Hormonal manipulation also has an important role in the treatment of **malignant neoplasms** of the breast (p. 702.1), prostate (p. 712.3), and endometrium (p. 704.3).

Hormonal Contraceptives

Anticonceptivos hormonales; Contraceptifs, Hormonaux; Hormonale Kontrazeptiva; Гормональный Контрацептивы

Types of Contraceptive

Hormonal contraceptives are currently only available for women although preparations for men are being evaluated. Oral hormonal contraceptives for women are divided into 2 main types: 'combined' (containing an oestrogen and a progestogen) and 'progestogen-only'. Parenteral preparations have also been developed and include subcutaneous implants and depot intramuscular injections. Progestogen-releasing intra-uterine devices and a combined hormonal contraceptive vaginal ring are available. A combined hormonal transdermal patch has also been developed.

Parenteral progestogen-only contraceptives provide reliable suppression of ovulation by suppressing the necessary mid-cycle surge of luteinising hormone. However, the low doses in progestogen-only oral contraceptives do not suppress it reliably in all cycles. Contraceptive efficacy is instead achieved by thickening the cervical mucus so that it is not readily penetrated by sperm, and by preventing proliferation of the endometrium so that it remains unfavourable for implantation of any fertilised ova. Intra-uterine progestogen-only devices act similarly; the physical presence of the system in the uterus may also contribute to overall contraceptive efficacy.

Oestrogens inhibit ovulation by suppressing the mid-cycle release of follicle-stimulating hormone. They act synergistically with progestogens in combined oral contraceptives to provide regular and consistent suppression of ovulation.

Oral preparations are also available for *emergency contraception* after unprotected coitus; they prevent implantation of any fertilised ova.

Uses and Administration

The main use of hormonal contraceptives is for contraception, but combined oral contraceptives are also commonly used in menstrual disorders such as dysmenorrhoea (p. 8.2), premenstrual syndrome (p. 2272.3), and menorrhagia (p. 2300.3), particularly where contraception is also required. Combined oral contraceptives are also used in polycystic ovary syndrome (p. 2253.3) and Turner's syndrome (p. 2254.3), and may be used in endometriosis (p. 2264.1); those containing non-androgenic progestogens may be used in acne (p. 2232.3) and hirsutism (p. 2262.1).

Combined oral contraceptives containing both an oestrogen and a progestogen are the most effective type of oral contraceptive for general use. The synthetic ethinyl derivative ethinylestradiol is the oestrogen typically used, although mestranol or estradiol valerate may be found in some preparations. The progestogenic component is usually a 19-nortestosterone derivative such as desogestrel, etynodiol diacetate, gestodene, levonorgestrel, lynestrenol, norethisterone, norethisterone acetate, norgestimate, or norgestrel. Other progestogenic compounds in use include chlormadinone acetate, dienogest, drospirenone, and nomegestrol acetate. Preparations may be *monophasic* (containing a fixed dose of oestrogen and progestogen), or *multiphasic* (when the dose of progestogen, or both the progestogen and oestrogen, are varied through the cycle). Multiphasic preparations are designed to mimic more closely the pattern of endogenous hormone secretion and may provide better cycle control than monophasic preparations. More rarely, *sequential* preparations are used, which contain an oestrogen alone for part of the cycle. Most combined oral contraceptives are taken for 21 days followed by an interval of 7 days when menstrual bleeding will occur. Some preparations include 21 active tablets plus 7 inert tablets to remove the need for counting days ('every day' preparations). Variations on this 28-day cycle include 22 days of active tablets followed by a 6-day interval for bleeding, and 24 days of active tablets followed by a 4-day interval. Long- or extended-cycle preparations are also available: some preparations may be taken continuously for 84 days, followed by 7 days of inert tablets or a lower dose of oestrogen alone (such as ethinylestradiol 10 micrograms).

The symbol † *denotes a preparation no longer actively marketed*

More recently, a preparation containing active tablets to be taken every day without any tablet-free interval has been introduced. The oestrogen content of most preparations is currently ethinylestradiol 20 to 40 micrograms daily; in some preparations a lower dose of 15 micrograms is used and in others up to 50 micrograms is available (even higher doses were often formerly used). A formulation containing the lowest dose of oestrogen compatible with good cycle control should be chosen, considering the following:

- *low-strength* preparations (ethinylestradiol 20 micrograms) are most appropriate for women with risk factors for cardiovascular disease (see under Precautions, p. 2241.2), provided a combined oral contraceptive is considered otherwise suitable
- *standard-strength* preparations (ethinylestradiol 30 or 35 micrograms or mestranol 50 micrograms if monophasic, or ethinylestradiol 30 to 40 micrograms if phased) are appropriate for most other women
- *high-strength* preparations (ethinylestradiol 50 micrograms) are generally used only in circumstances where bioavailability of the oestrogen is reduced, such as concomitant use of some enzyme-inducing drugs (see Interactions, p. 2242.3)

Of the progestogens used in combined oral contraceptives, desogestrel, drospirenone, and gestodene may be useful for women who have adverse effects, such as acne, headache, depression, weight gain, breast symptoms, or breakthrough bleeding, with other progestogens. However, desogestrel and gestodene have been associated with an increased risk of venous thromboembolism (see p. 2238.1), and drospirenone should not be used in women at risk of hyperkalaemia.

When first **starting** combined oral contraceptives, if the first tablet is taken on the first day of the menstrual cycle (the first day of bleeding) additional contraceptive precautions are unnecessary. If the first tablet is taken on the fourth day of the cycle or later, additional contraceptive precautions should be undertaken for 7 days (or 14 days for 'every day' preparations in case the inert tablets are inadvertently taken first). If amenorrhoea is present and pregnancy has been excluded, combined oral contraceptives may be started on any day, but additional precautions should be used for the first 7 days. In the case of abortion or miscarriage combined oral contraceptives should be started on the same day. In women not breast feeding, they may be started 3 weeks postpartum, but additional contraceptive precautions should be taken for the first 7 days if the combined oral contraceptive is started later than 3 weeks postpartum; progestogen-only contraceptives are preferred in breast-feeding women (see under Precautions, p. 2241.1).

When **changing** to a combined preparation containing a different progestogen, the new preparation should be started on the day after the last active tablet of the old preparation. If a tablet-free interval is taken then extra contraceptive precautions are necessary for the first 7 days of the new preparation. In the case of 'every day' preparations, to allow for the fact that the inert tablets may inadvertently be taken first, extra contraceptive precautions are necessary during the first 14 days. Meticulous regularity of dosage is essential and contraceptive protection may be lost if a dose is not taken at the proper time or is missed, especially if the missed dose is at the beginning or end of a cycle.

If a tablet is **missed** the risk of pregnancy is greatest when this happens at the beginning or at the end of a cycle, which lengthens the tablet-free interval. Over time, advice for dealing with missed tablets has changed and varies between countries and preparations. In 2004, WHO issued recommendations based on how many combined oral contraceptive tablets have been missed and when.

- If 1 or 2 tablets containing 30 or 35 micrograms of ethinylestradiol (or 1 tablet of 20 micrograms) have been missed at any time, the most recent missed tablet should be taken as soon as possible, and the rest of the course should be taken as normal; no additional contraceptive protection or emergency contraception is needed. This advice also applies if a new course of tablets has been started 1 or 2 days late for 30- or 35-microgram tablets, or 1 day late for 20-microgram tablets.
- If 3 or more tablets containing 30 or 35 micrograms of ethinylestradiol (or 2 or more tablets of 20 micrograms) have been missed at any time, the most recent missed tablet should be taken as soon as possible, and the rest of the course should be taken as normal; the woman should also use condoms or abstain from intercourse until she has taken active tablets for 7 days in a row. This advice also applies if a new course of tablets has been started 3 or more days late for 30- or 35-microgram tablets, or 2 or more days late for 20-microgram tablets. In addition, emergency contraception should be considered if the tablets were missed in the first week of the course and she had unprotected intercourse during the tablet-free interval or in the first week. If the tablets were missed in the third week of the course, then the tablet-free interval (or the 7 inert tablets) should be omitted and the next course of tablets started immediately after the last.

If the woman has missed more than 1 tablet, she can take the first missed tablet and then either continue taking the rest of the missed tablets or discard them to stay on schedule. Depending on when she realises that she has missed a tablet, she may take 2 tablets on the same day or even at the same time.

For extended-cycle preparations, licensed product information gives similar advice regarding missed tablets (or starting a course late), in that the course should be resumed as soon as possible. If 1 tablet has been missed, additional contraception is not needed, but if 2 or more tablets have been missed, additional contraception should be used until 7 days of active tablets have been taken.

Similarly, extra contraceptive measures may be needed during, and after recovery from, vomiting or diarrhoea. WHO recommends that if the woman vomits within 2 hours after taking a tablet, she should take another tablet. If there is severe vomiting or diarrhoea for more than 24 hours she should continue taking the course if she can, and if it continues for 2 or more days she should follow the advice for missed tablets.

Licensed product information for some multiphasic sequential preparations may offer advice regarding additional contraceptive precautions that differs from these general recommendations.

Progestogen-only oral contraceptives are suitable for women when an oestrogen component is contra-indicated. They are taken continuously, usually **starting** on day one of the menstrual cycle, with no interval during menstrual bleeding. They are associated with a higher failure rate than the combined preparations. Regularity in taking the doses is even more important with this type of preparation; contraceptive efficacy is reduced if a dose is delayed by more than 3 hours (a delay of up to 12 hours is acceptable for desogestrel). Commonly used progestogens include the 19-nortestosterone derivatives etynodiol diacetate, levonorgestrel or norgestrel, and norethisterone.

When **changing** from a combined oral contraceptive preparation to an oral progestogen-only contraceptive, the new tablets should be started immediately with no tablet-free interval (or, in the case of 'every day' preparations, omitting the inert tablets).

If a **missed tablet** is delayed by more than 3 hours (or 12 hours for desogestrel), it should be taken as soon as possible and the next tablet taken at the correct time. Although some UK licensed product information suggests that additional contraceptive methods should be used for the next 7 or 14 days, depending on the product, WHO suggests that extra contraception is only required for the next 2 days. Emergency contraception should be considered if unprotected intercourse has occurred before 2 further tablets have been taken correctly. Additional contraceptive methods may also be needed during, and after recovery from, vomiting or diarrhoea, and WHO gives the same advice as that for combined oral contraceptives described above.

Progestogens are also used alone as **parenteral contraceptives** and provide a very high level of contraceptive efficacy. They are usually given within the first 5 days of the menstrual cycle. Injectable contraceptives are usually used to provide short-term protection for several months or are used in women unable to use other methods. Medroxyprogesterone acetate is given by intramuscular or subcutaneous injection as a long-acting depot preparation to provide contraception for at least 12 weeks. Norethisterone enantate is used similarly by intramuscular injection to provide protection for up to 8 weeks. Levonorgestrel is used in the form of a subcutaneous implant providing contraception for up to 5 years. A contraceptive implant containing etonogestrel, effective for 3 years, is also available. A combined parenteral contraceptive containing the oestrogen estradiol cipionate with medroxyprogesterone acetate, and given monthly by intramuscular injection, has been developed.

Intra-uterine contraceptive devices that release levonorgestrel can provide contraception for 3 or 5 years, depending on the device. They are usually inserted within 7 days of the onset of menstruation, or immediately after first trimester termination of pregnancy. To reduce the risk of uterine perforation, insertion postpartum or after second trimester termination should be delayed for at least 6 weeks, and until the uterus is fully involuted. A contraceptive **vaginal ring**, which releases ethinylestradiol and etonogestrel, is retained in the vagina for 3 weeks; it is then removed for a one-week interval after which a new ring is inserted.

A contraceptive **transdermal patch**, which releases ethinylestradiol and norelgestromin, has been developed. A new patch is applied each week for 3 weeks, followed by a one-week patch-free interval. If the patch becomes partly or completely detached, or there is a delay in its application, contraceptive efficacy can be reduced or lost.

- If the patch has been detached for less than 24 hours, it should be re-applied if it is still sufficiently adhesive, or replaced with a new patch; no additional contraceptive method is needed and the following patch should be applied on the usual day. If it has been detached for 24 hours or more, a new 4-week cycle should be started and a new patch applied; additional contraceptive precautions should be taken for the first 7 days.
- If application of the first patch of a new cycle is delayed after the patch-free interval, it should be applied as soon as remembered and this day used as the first day of the new cycle; additional contraceptive precautions should be used for 7 days, and if unprotected intercourse has occurred during the patch-free interval then the possibility of fertilisation should be considered.
- When the patch is changed in the middle of the cycle (week 2 and 3), if there is a delay of up to 48 hours the new patch should be applied immediately, with the next patch applied on the usual day; no additional contraceptive precaution is needed. If the delay is more than 48 hours, the new patch should be applied and a new 4-week cycle started; additional contraceptive precautions should be taken for 7 days.
- If there is a delay in removing the third patch, before the patch-free interval, it should be removed as soon as possible and the next cycle started on the usual day; no additional contraception is required.

Postcoital hormonal contraceptives (emergency contraception) should be taken within 72 hours after unprotected intercourse to be most effective (for details see Emergency Contraception, p. 2233.2). A single oral dose of levonorgestrel 1.5 mg may be given within 72 hours of intercourse, or it may be given as a dose of 750 micrograms within 72 hours of intercourse followed by a second dose 12 hours later. An alternative preparation available for such use consists of tablets each containing ethinylestradiol 50 micrograms and levonorgestrel 250 micrograms. Two tablets should be taken within 72 hours and a further 2 tablets 12 hours later. UK licensed product information for levonorgestrel-only preparations suggests that if vomiting occurs within 3 hours of any dose it can be repeated. However, WHO considers that 2 hours is probably sufficient for hormone absorption and that no action is needed if vomiting occurs after this time. WHO also considers that combined hormonal preparations are more likely to cause nausea and vomiting, and that the use of an antiemetic may be considered before repeating a dose. The efficacy of postcoital emergency contraception may be reduced in women who are being treated with enzyme-inducing drugs, and a higher dose of levonorgestrel has been suggested (see Interactions, p. 2242.3).

Reviews and guidelines.

1. Department of Reproductive Health and Research. *Selected practice recommendations for contraceptive use*. 2nd ed. Geneva: WHO, 2004. Also available at: http://whqlibdoc.who.int/publications/2004/9241562846.pdf (accessed 14/01/08)
2. Wiegratz I, Kuhl H. Long-cycle treatment with oral contraceptives. *Drugs* 2004; 64: 2447–62.
3. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Missed pills: new recommendations. *J Fam Plann Reprod Health Care* 2005; 31: 153–5. Also available at: http://www.ffprhc.org.uk/admin/uploads/MissedPillRules%20.pdf (accessed 14/01/08)
4. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (April 2006): emergency contraception. *J Fam Plann Reprod Health Care* 2006; 32: 121–7. Also available at: http://www.ffprhc.org.uk/admin/uploads/449_EmergencyContraceptionCEUguidance.pdf (accessed 14/01/08)
5. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (issued July 2006, updated January 2007): first prescription of combined oral contraception. Available at: http://www.ffprhc.org.uk/admin/uploads/FirstPrescCombOralContJan06.pdf (accessed 14/01/08)
6. Spencer AL, *et al*. Helping women choose appropriate hormonal contraception: update on risks, benefits, and indications. *Am J Med* 2009; 122: 497–506.

Acne. Oral contraceptives have been shown to be effective[1,2] in reducing inflammatory and non-inflammatory lesions in women with acne (p. 1682.2) who require contraception, probably by a multifactorial action on circulating androgens. Studies have used combinations of ethinylestradiol with various progestogens; a systematic review[2] considered that combinations with chlormadinone acetate or cyproterone acetate were more effective than those with levonorgestrel, but noted that this was based on limited evidence. Combination preparations based on cyproterone acetate, that also have a contraceptive effect, are generally reserved for the management of moderate to severe acne in women with signs of hyperandrogenism (see also p. 2261.3).

1. Huber J, Walch K. Treating acne with oral contraceptives: use of lower doses. *Contraception* 2006; 73: 23–9.
2. Arowojolu AO, *et al*. Combined oral contraceptive pills for treatment of acne. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2012 (accessed 19/12/13).

Contraception. Contraception is used for fertility control, and some methods have additional non-contraceptive health benefits. There are many regular methods including periodic abstinence (natural family planning), male and female barrier methods, intra-uterine devices (IUDs), female hormonal contraceptives, and female or male steri-

lisation. In addition, female hormonal contraceptives and copper IUDs are available for emergency (postcoital) contraception. The methods used for contraceptive purposes can be grouped into three categories: those that prevent ovulation, those that prevent fertilisation of the ovum, and those that prevent implantation of the fertilised ovum. None of the available contraceptive methods are effective once implantation of a fertilised ovum has occurred, i.e. they are not abortifacients.

A large number of factors will influence the choice of contraceptive method. Those relating to the woman include age (and therefore likely fertility), parity, medical disorders, risk of sexually transmitted diseases, smoking status, breast feeding, and cultural and religious considerations. Those relating to the method include its failure rate, reversibility, ease of use, mechanism of action, adverse effects, and non-contraceptive benefits.

The most reliable reversible methods for contraception are those for which there can be no 'user' failure such as *progestogen injections* and *implants*, and progestogen or copper *intra-uterine devices* (IUDs). When used perfectly, these methods have reported failure rates of between 0.05 and 0.6% during the first year of use; higher rates had been reported with older IUDs. The duration of action of the various progestogen injections is up to 2 or 3 months, whereas progestogen implants and progestogen IUDs can be effective for 1 to 5 years, depending on the preparation. These long-acting progestogen preparations thicken cervical mucus, so preventing sperm penetration, and suppress the endometrium, so preventing implantation. In addition, they suppress ovulation; the degree of suppression is complete for injectable preparations, about 50% for implants, and low for the progestogen IUDs. Copper IUDs were traditionally thought to act by preventing implantation, but it is now thought that the biochemical changes which they produce in the uterus also prevent fertilisation. They are effective and have a prolonged action (up to 5 or 10 years). There is an increased risk of pelvic infection in the 20 days after insertion of an IUD, but the risk is the same as non-IUD users thereafter. An IUD must not be used in women with a current sexually transmitted infection or pelvic inflammatory disease, but it may be considered in those who are no longer at risk after an infection has been treated. For women at increased risk of infection, prophylactic antibacterial therapy may be given before IUD insertion if screening test results are not yet available. In the past, it was recommended that IUDs were not suitable for nulliparous women because of a risk of impaired fertility after removal. However, this may have been biased by other factors such as the increased risk of sexually transmitted infection associated with sexual behaviour in younger women. Nulliparity alone is therefore no longer considered a contra-indication to IUD use, and indeed some IUDs have been designed specifically for this group of women. Although IUDs are effective at preventing pregnancy, in the uncommon event of IUD failure, the risk of ectopic pregnancy is increased and can occur in 6 to 8% of these pregnancies.

Of methods subject to 'user' failure, *combined oral contraceptives* are the most effective. They have a reported failure rate during the first year of 0.3% if used perfectly, but 8% in typical practice. Their principal mechanism of action is to prevent ovulation, and they also decrease the chances of fertilisation and implantation. Combined oral contraceptives offer the non-contraceptive advantages of avoidance of dysmenorrhoea, premenstrual tension, and iron-deficiency anaemia, and in the long-term they protect against endometrial and ovarian cancer. However, they do not protect against sexually transmitted diseases, they are unsuitable for older women who smoke, and long-term use carries a slight increased risk of breast cancer. Other forms of combined contraceptive which have been developed recently include *monthly injection*, *vaginal ring*, and *transdermal patch*.

Progestogen-only oral contraceptives are considered to have a slightly higher failure rate than that for combined preparations because of the need for more accurate dosage timing. A 0.9% failure rate has been given for the first year of use if taken correctly, but in practice failure rates of up to 10% have been reported. Failure rates are lower in women taking these contraceptives during breast feeding, as breast feeding itself provides additional contraception (see also Natural Family Planning Methods, below). Regularity in taking them is essential; a dose should not be delayed for more than 3 hours (up to 12 hours for desogestrel). They act mainly to decrease the chance of fertilisation and implantation since they prevent ovulation in only 14 to 50% of cycles, although desogestrel is said to reliably inhibit ovulation. They are useful for women who are breast feeding, for those who smoke and are more than 35 years of age, and if medical conditions contra-indicate the use of oestrogens.

Barrier methods, including both male and female condoms, vaginal sponges containing spermicide, and diaphragms and cervical caps used with spermicide, act as a mechanical barrier to prevent fertilisation, and inactivate sperm. Barrier methods decrease the risk of sexually transmitted diseases and a shift towards their use has occurred since the emergence of HIV infection in particular. However, barrier methods are not as effective in preventing conception as hormonal contraception and IUDs. Even when used correctly, failure rates in the first year of use vary from 2% for the male condom, to 6% for the diaphragm with spermicide, to 20% for the vaginal sponge in parous women. Spermicides, such as nonoxinol 9, may be used as foam, cream, jelly, dissolvable vaginal tablets or pessaries, or as a spermicide-containing polyvinyl alcohol film placed over the cervix. However, they are generally considered relatively ineffective when used as the sole method of contraception, and such use is not recommended.

Natural family planning methods such as periodic abstinence using the calendar, temperature, cervical mucus ('Billings') or sympto-thermal methods require high motivation to learn and practice effectively. However, they may be the only acceptable method to some people. More recently, daily measurement of urine hormone concentrations has been used as a predictor of the timing of ovulation and hence the risk of becoming pregnant; on 'unsafe' days abstinence or barrier methods are required. Traditional methods such as withdrawal (coitus interruptus) are widely used in some areas, but are considered relatively ineffective. The lactational amenorrhoea method of contraception can be used during breast feeding for up to 6 months after childbirth. For it to be an effective contraceptive method, breast feeding must start immediately after birth, the infant must be fully or nearly fully breast-fed, feedings must be no more than 4 to 6 hours apart, and menstruation must not have restarted. When carried out consistently and correctly, this method has a failure rate of 0.9% in the first 6 months.

Various other methods of contraception are under investigation including the use of the antiprogestogen mifepristone, selective sex-hormone receptor modulators, and contraceptive vaccines. There has also been some investigation of **male contraception**. Weekly intramuscular injection of high-dose testosterone or nandrolone to produce azoospermia has been investigated with some success, but development of an oral contraceptive dosage form for males has been slow. Use of a progestogen with testosterone is being studied, as is the use of implants of synthetic androgens such as trestolone (7-α-methyl-19-nortestosterone; MENT).

The available irreversible methods of contraception are surgical male or female *sterilisation*. The use of mepacrine for non-surgical female sterilisation has been attempted but has proved extremely controversial.

References.

1. Beifield T. *FPA Contraceptive Handbook: a guide for family planning and other health professionals*. 3rd ed. London: Family Planning Association, 1999.
2. Baird DT, Glasier AF. Contraception. *BMJ* 1999; 319: 969–72.
3. Baird DT. Overview of advances in contraception. *Br Med Bull* 2000; 56: 704–16.
4. Anderson RA. Hormonal contraception in the male. *Br Med Bull* 2000; 56: 717–28.
5. Lähteenmäki P, Jukarainen H. Novel delivery systems in contraception. *Br Med Bull* 2000; 56: 739–48.
6. Kubba A, *et al*. Contraception. *Lancet* 2000; 356: 1913–19.
7. Foran TM. New contraceptive choices across reproductive life. *Med J Aust* 2003; 178: 616–20.
8. The ESHRE Capri Workshop Group. Hormonal contraception without estrogens. *Hum Reprod Update* 2003; 9: 373–86.
9. Graesslin O, Quereux C. Mise au point sur la contraception. *J Gynecol Obstet Biol Reprod (Paris)* 2005; 34: 529–56.
10. National Collaborating Centre for Women's and Children's Health/NICE. Long-acting reversible contraception (issued October 2005). Available at: http://guidance.nice.org.uk/CG30/niceguidance/pdf/English (accessed 14/01/08)
11. Naz RK. Contraceptive vaccines. *Drugs* 2005; 65: 593–603.
12. Peterson HB, Curtis KM. Long-acting methods of contraception. *N Engl J Med* 2005; 353: 2169–75.
13. Hoesl CE, *et al*. Reversible, non-barrier male contraception: status and prospects. *Eur Urol* 2005; 48: 712–22.
14. David PS, *et al*. Hormonal contraception update. *Mayo Clin Proc* 2006; 81: 949–55.
15. Amory JK, *et al*. Drug insight: recent advances in male hormonal contraception. *Nat Clin Pract Endocrinol Metab* 2006; 2: 32–41.
16. Liu PY, *et al*. Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. *Lancet* 2006; 367: 1412–20.
17. WHO, John Hopkins Bloomberg School of Public Health, United States Agency for International Development. Family planning: a global handbook for providers (2007, updated April, 2008). Available at: http://info.k4health.org/globalhandbook/ (accessed 21/07/10)
18. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. FSRH guidance (November 2007): intrauterine contraception. Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceIntrauterineContraceptionNov07.pdf (accessed 09/07/08)

Emergency contraception. Emergency contraception (postcoital contraception) can be used after unprotected intercourse but before a fertilised ovum has been implanted. Methods that act after implantation are considered abortifacients. The two most commonly used emergency contraceptives are *oral contraceptives* and *copper IUDs*.

Oral hormonal contraceptive regimens (the so-called 'morning after pill') have historically used a preparation containing high-dose oestrogen with a progestogen, taken within 72 hours of intercourse, and repeated 12 hours later (the Yuzpe regimen). This preparation is thought to act by a variety of mechanisms, which may depend on when in the menstrual cycle it is used. It may prevent implantation, prevent or delay ovulation, disrupt ovum transport, and alter corpus luteum function. However, levonorgestrel alone (without an oestrogen) is now widely recommended as an emergency contraceptive. A large WHO multicentre study found that levonorgestrel 750 micrograms alone within 72 hours of intercourse and repeated after 12 hours was more effective than the Yuzpe regimen and better tolerated.[1] Both regimens were most effective when given within 24 hours of intercourse.[1,2] A small observational study[3] of the Yuzpe method used between 72 and 120 hours after unprotected intercourse reported a trend towards decrease in efficacy. A further large study[4] by WHO found that for up to 120 hours after intercourse, a single dose of levonorgestrel 1.5 mg was as effective as two doses of 750 micrograms given 12 hours apart, with a pregnancy rate of about 1.5%.

Efficacy rates vary between studies, but the Yuzpe method has been shown to reduce the risk of pregnancy by about 75% and levonorgestrel by about 89%.[5] Based on its greater efficacy and better tolerability, levonorgestrel is now generally recommended as the hormonal emergency contraceptive of choice that can be offered up to 120 hours after intercourse.[5–9]

Copper, but not progestogen, IUDs can be inserted up to 120 hours after unprotected intercourse for postcoital contraception. They have a failure rate of no more than 1% when used for emergency contraception.[9] Thus, when efficacy is a priority the IUD is the emergency contraceptive method of choice.

The *antiprogestogen* mifepristone is under investigation as an emergency contraceptive. Its action appears to depend on inhibiting ovulation or, if ovulation has occurred, preventing implantation. Mifepristone also appears to be at least as effective as levonorgestrel but it can delay the onset of subsequent menstruation, which might cause anxiety in some women.[10,11] Another drug with antiprogestogen effects, the progesterone receptor modulator ulipristal acetate, may be at least as effective as levonorgestrel.[12,13] It can be used up to 120 hours after intercourse, but it is yet to become established for emergency contraception.

1. Task Force on Postovulatory Methods of Fertility Regulation. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet* 1998; 352: 428–33.
2. Piaggio G, *et al*. Timing of emergency contraception with levonorgestrel or the Yuzpe regimen. *Lancet* 1999; 353: 721.
3. Rodrigues I, *et al*. Effectiveness of emergency contraceptive pills between 72 and 120 hours after unprotected sexual intercourse. *Am J Obstet Gynecol* 2001; 184: 531–7.
4. von Hertzen H, *et al*. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002; 360: 1803–10.
5. Dunn S, Guilbert E, Society of Obstetricians and Gynaecologists of Canada. Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guidelines no. 131, August 2003: Emergency contraception. *J Obstet Gynaecol Can* 2003; 25: 673–9. Also available at: http://www.sogc.org/guidelines/public/131E-CPG-August2003.pdf (accessed 14/01/08)
6. WHO. Emergency contraception (fact sheet no 244, revised October 2005). Available at: http://www.who.int/mediacentre/factsheets/fs244/en/print.html (accessed 14/01/08)
7. American College of Obstetricians and Gynecologists. ACOG practice bulletin number 69, December 2005: emergency contraception. *Obstet Gynecol* 2005; 106: 1443–52.
8. American Academy of Pediatrics Committee on Adolescence. Emergency contraception. *Pediatrics* 2005; 116: 1026–35. Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;116/4/1026.pdf (accessed 14/01/08)
9. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, FFPRHC guidance (April 2006): emergency contraception. *J Fam Plann Reprod Health Care* 2006; 32: 121–8. Also available at: http://www.ffprhc.org.uk/admin/uploads/449_EmergencyContraceptionCEUguidance.pdf (accessed 14/01/08)
10. Sarkar NN. The potential of mifepristone (RU-486) as an emergency contraceptive drug. *Acta Obstet Gynecol Scand* 2005; 84: 309–16.
11. Cheng L, *et al*. Interventions for emergency contraception. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/07/08).
12. Creinin MD, *et al*. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. *Obstet Gynecol* 2006; 108: 1089–97.
13. Glasier AF, *et al*. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. *Lancet* 2010; 375: 555–62.

Malignant neoplasms. The prophylactic use of oral contraceptives may protect against ovarian cancer in women with mutations of the BRCA1 or BRCA2 genes, but must be balanced against the risk of breast cancer in these women (see Ovary, under Carcinogenicity, p. 2236.1).

Adverse Effects

Many reports have been published of adverse effects associated with the use of **combined oral contraceptives**. The data have mostly been gained retrospectively and often involve older preparations containing higher doses of oestrogen and progestogen than are used currently. A similar spectrum of adverse effects has also been reported for

combined hormonal contraceptives administered transdermally and vaginally.

There may be gastrointestinal adverse effects such as nausea or vomiting, chloasma (melasma) and other skin or hair changes, headache, water retention, weight gain, breast tenderness, and changes in libido.

Menstrual irregularities such as spotting, breakthrough bleeding, or amenorrhoea can occur during treatment. These effects may result from the relative balance of oestrogenic and progestogenic effects of particular products and their incidence may be reduced by changing to a different product. For example, early or mid-cycle spotting or absence of withdrawal bleeding may require a preparation with a greater oestrogen to progestogen ratio or less progestogen as in multiphasic preparations.

Intolerance to contact lenses has been reported and vision may deteriorate in myopic patients. Some patients may develop depression and other mental changes. Preparations containing a progestogen with androgenic properties such as levonorgestrel or norgestrel may be associated with increased oiliness of the skin and acne. Conversely, acne may be improved with progestogens such as norgestimate or desogestrel.

There is an increased risk of cardiovascular disease and associated mortality related, at least in part, to the oestrogen content of combined oral contraceptives. The incidence of cardiovascular adverse effects is probably less with the newer lower-dose preparations than with the older higher-dose preparations. Increased mortality from myocardial infarction is much greater with increased age and in cigarette smokers, although some evidence suggests that healthy women aged over 35 years who do not smoke are not at increased risk. Other risk factors include a family history of arterial disease, diabetes mellitus, hypertension, obesity, and migraine. Thrombosis may be more common when factor V Leiden is present or in patients with blood groups A, B, or AB. Specific risk factors for venous thromboembolism include varicose veins, long-term immobilisation, obesity, and a family history of venous thromboembolism. Recent evidence has also indicated that the risk of venous thromboembolism varies according to the progestogen component of combined oral contraceptives; a higher incidence has been associated with desogestrel and gestodene than with levonorgestrel, norethisterone, and etynodiol. For further discussion see Venous Thromboembolism, p. 2238.1.

Combined oral contraceptives may cause hypertension and there may be reduced glucose tolerance and changes in lipid metabolism. Liver function can be impaired, although jaundice is rare. There appears to be a marked increase (though the incidence is still very low) in the relative risk of benign liver tumours. Malignant liver tumours have also been reported.

Combined oral contraceptives are reported to slightly increase the risk of cervical cancer (although other factors may be involved) and breast cancer, but to protect against ovarian cancer and endometrial cancer. For further discussion, see Carcinogenicity, below.

As with combined oral contraceptives, **progestogen-only contraceptives** may cause nausea, vomiting, headache, breast discomfort, depression, skin disorders, and weight gain. Menstrual irregularities such as amenorrhoea, breakthrough bleeding, spotting, and menorrhagia are more common with progestogen-only contraceptives, and are particularly common with parenteral preparations. Ovarian cysts are also common in women using progestogen-only contraceptives, since they do not prevent ovulation in all cycles and may delay follicular atresia. These enlarged follicles usually disappear spontaneously, but are sometimes associated with pelvic pain or dyspareunia. Available progestogen-only contraceptives carry less risk of thromboembolic and cardiovascular disease than combined oral contraceptives.

Carcinogenicity. Concern has often been expressed as to whether the use of hormonal contraceptives by normally healthy women may either cause or increase the risk of developing malignant neoplasms. To investigate any possible link between such use and cancer, two main types of study have been used by epidemiologists, namely the prospective study and the case-control study. Many factors have made direct comparison of results difficult and such factors include the type and composition of oral contraceptive used (which has changed over the years), the age of the patient, the age at which use first began, and the sexual and obstetric history of the patient. Overall the evidence indicates that combined oral contraceptives in fact exert a protective effect against the development of endometrial and ovarian carcinoma. However, there is a small increase in risk of breast cancer during use and for 10 years after discontinuation. In addition, there does appear to be a slight risk of cervical cancer with the prolonged use of combined oral contraceptives and a negligible risk of liver cancer. For further details concerning the effects on individual organs, see the following sections. It should be noted that even where the relative risk has been shown to be substantially increased this will not translate into many new cases of a rare cancer, and this contributes to the difficulties of assessing clinical relevance.

In the long-term Oxford Family Planning Association contraceptive study, the beneficial effects of oral contraceptives on the uterus and ovary were calculated to outweigh the adverse effect on the cervix.[1] This large cohort study also found no increased risk of breast cancer although the data could not exclude a small increase in risk with current use that declined after stopping. Long-term follow-up of the prospective Royal College of General Practitioners' study has found no overall increased risk of cancer.[2] It is also worthy of note that two large prospective cohort studies (the Nurses' Health Study and the Royal College of General Practitioners' study) found no evidence of a difference in overall mortality between women who had used oral contraceptives and those who had not.[3,4] Some general reviews on hormonal contraceptives and cancer are cited below.[5-9]

1. Vessey M, Painter R. Oral contraceptive use and cancer: findings in a large cohort study, 1968–2004. *Br J Cancer* 2006; 95: 385–9.
2. Hannaford PC, *et al.* Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. Abridged version: *BMJ* 2007; 335: 651–4. Full version: http://www.bmj.com/cgi/reprint/335/7621/651.pdf (accessed 14/01/08)
3. Colditz GA, *et al.* Oral contraceptive use and mortality during 12 years of follow-up: the Nurses' Health Study. *Ann Intern Med* 1994; 120: 821–6.
4. Beral V, *et al.* Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *BMJ* 1999; 318: 96–100.
5. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
6. La Vecchia C, *et al.* Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 1996; 14: 260–72.
7. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; 24: 741–54.
8. Lech MM, Ostrowska L. Risk of cancer development in relation to oral contraception. *Eur J Contracept Reprod Health Care* 2006; 11: 162–8.
9. IARC/WHO. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. *IARC monographs on the evaluation of carcinogenic risks to humans volume 91* 2007. Available at: http://monographs.iarc.fr/ENG/Monographs/vol91/mono91.pdf (accessed 20/07/10)

BREAST. Many epidemiological studies have been published on the potential link between hormonal contraceptives and breast cancer. Most of these data relate to **combined oral contraceptives**, which are the most widely used form. The breast cancer risk from use of these contraceptives will require monitoring for some time to come as the first users of oral contraceptives continue to age, and because of the changing patterns of use.

Early studies from the 1980s variously failed to show any significant increase in risk of breast cancer in women who had ever used hormonal contraceptives compared with those who had never done so,[1-4] or showed an increase in risk,[5] or identified a risk in specific sub-groups of users.[6-12] Potential identified risk factors, for which much of the evidence was conflicting, included current use,[10] duration of use,[7,11] age at first use,[6] duration of use before a first full-term pregnancy,[7,8] nulliparity,[9] high-dose preparations,[11] and family history of breast cancer.[12] It was also reported that use of oral contraceptives might lead to an accelerated presentation of breast cancer,[13] or an increased risk of invasive cancer.[4]

In response to these studies, the UK CSM,[14] the FDA in the USA,[15] and the International Committee for Research in Reproduction[16] issued advice that the available evidence did not require a change in prescribing practice. This advice has not been subsequently changed, although patients should be informed of the possible small increase in risk of breast cancer, which has to be weighed against established benefits of therapy.[17]

A Collaborative Group on Hormonal Factors in Breast Cancer was set up to re-analyse all the worldwide epidemiological evidence on breast cancer risk and hormonal contraceptives. The group identified individual data on 53 297 women with breast cancer, and 100 239 controls (women without breast cancer) from 54 studies, and published a summary of their findings,[18] and a further detailed review.[19] They reported that women currently using oral contraceptives have a slight increase in the relative risk of breast cancer (1.24; 95% confidence intervals 1.15 to 1.33), and that this risk decreases after stopping use, and is no longer significant after 10 or more years. There was a weak trend towards an increase in risk with increasing duration of use. Thus, it appears that the risk of breast cancer

- increases soon after first exposure
- does not increase with duration of exposure
- returns to normal 10 years after cessation of exposure.[18]

Reviews[20,21] of major studies published between 1990 and 2000, including that of the Collaborative Group, have also indicated that, in general, there is some excess breast cancer risk in current or recent users of oral contraceptives, but that excess risk does not persist in the long term after cessation of oral contraceptive use, regardless of duration of use.

The Collaborative Group found that cancers diagnosed in those who had ever used hormonal contraceptives were clinically less advanced than in those who had never done so.[18] Further information is required on whether this is related to earlier diagnosis or a biological effect of the hormones. In addition, data on breast cancer mortality are required.

When analysed by *age at first use*, the risk was largest in those women who started use as teenagers. Because of the trend towards earlier use, further review of long-term data is required.[18] The most important risk factor is, however, the *age at which women discontinue* the contraceptive; the greater the age at stopping, the more breast cancers are diagnosed.[17]

Data from the collaborative group suggested that there was no difference in risk with *parity* when comparing nulliparous women, parous women who began use of oral contraceptives before their first child, and parous women who began use of oral contraceptives after the birth of their first child.[18] However, a later meta-analysis[22] reported higher risks in parous women, particularly those who used oral contraceptives for 4 or more years before first full-term pregnancy.

Low-dose oral contraceptives were not associated with a decreased risk of breast cancer.[18] When preparations were grouped according to oestrogen dose (< 50 micrograms, 50 micrograms, and > 50 micrograms), there was, if anything, a decrease in breast cancer risk with increasing dose among women who had stopped use 10 or more years before, largely due to a reduction in breast cancer risk in those who had used the highest dose preparations.

The Collaborative Group's analysis did not note any difference in risk according to *family history*.[18] However, a subsequent cohort study found an increased risk of breast cancer among women with a strong family history of the disease who used earlier formulations of oral contraceptives.[23] Another cohort study[24] provided support for the Collaborative Group's findings, reporting no statistical difference in the risk with oral contraceptive use in women with a family history of breast cancer; there was actually a trend towards a reduction in risk of breast cancer with long-term use. Women carrying mutations in the BRCA1 or BRCA2 genes are at increased risk of developing breast cancer; any additional risk from oral contraceptives is of particular concern because these women may be encouraged to take them to reduce their risk of ovarian cancer (see Ovary, p. 2236.1). However, results from studies in known carriers of these mutations have been mixed. A modest increase in the risk of breast cancer in BRCA1 carriers has been reported with ever use of oral contraceptives,[25] but another study[26] found a reduced risk in carriers who used current preparations containing lower oestrogen doses than those available before 1975. Further study is needed in these women.

There are far fewer data on risk of breast cancer with **progestogen-only contraceptives**, which are less frequently used than combined preparations.

A WHO study published in 1991 indicated that, overall, depot medroxyprogesterone acetate did not increase the risk of breast cancer (relative risk compared with never users 1.21; 95% confidence intervals 0.96 to 1.53) and that risk did not increase with duration of use.[27] However, there appeared to be a slight increase in risk within the first 4 years of use, especially in women under 35 years of age. These findings agreed with those of a smaller study[28] in which women who had used depot medroxyprogesterone acetate for 2 years or longer before the age of 25 had a relative risk of 4.6. Pooled analysis of these 2 studies indicated that current or recent use was the key factor.[29] The relative risk of breast cancer in women who had used medroxyprogesterone acetate in the last 5 years was 2.0, and there was no increased risk in women who had ceased use more than 5 years previously, regardless of their duration of use. Another small study[30] reported no increase in risk overall in women who had ever used medroxyprogesterone acetate; there was an increase for current use in the subgroup of women aged 35 to 44 (relative risk 2.3), but this was no longer the case 4 years after stopping.

The Collaborative Group on Hormonal Factors in Breast Cancer reported that there was some evidence of an increased risk of breast cancer for use of oral or injectable progestogens in the previous 5 years (relative risk 1.17), and no risk 10 or more years after stopping use.[18] These findings were broadly similar to those for combined preparations. As for combined preparations, the most important factor is the *age at discontinuation*. For women who stop by age 30 after 5 years use of a progestogen-only preparation there would be an estimated increase from 44 to 46 or 47 cases per 10 000 compared with those who have never used a hormonal contraceptive. For 5 years use stopping by age 40 there would be an estimated increase from 160 to 170 cases diagnosed in the following 10 years.[17]

1. Ellery C, *et al.* A case-control study of breast cancer in relation to the use of steroid contraceptive agents. *Med J Aust* 1986; 144: 173–6.

2. Paul C, *et al.* Oral contraceptives and breast cancer: a national study. *BMJ* 1986; 293: 723–6.
3. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. Oral-contraceptive use and the risk of breast cancer. *N Engl J Med* 1986; 315: 405–11.
4. Stanford JL, *et al.* Oral contraceptives and breast cancer: results from an expanded case-control study. *Br J Cancer* 1989; 60: 375–81.
5. Miller DR, *et al.* Breast cancer before age 45 and oral contraceptive use: new findings. *Am J Epidemiol* 1989; 129: 269–80.
6. Pike MC, *et al.* Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. *Lancet* 1983; ii: 926–30.
7. Meirik O, *et al.* Oral contraceptive use and breast cancer in young women: a joint national case-control study in Sweden and Norway. *Lancet* 1986; ii: 650–4.
8. McPherson K, *et al.* Early oral contraceptive use and breast cancer: results of another case-control study. *Br J Cancer* 1987; 56: 653–60.
9. Meirik O, *et al.* Breast cancer and oral contraceptives: patterns of risk among parous and nulliparous women—further analysis of the Swedish-Norwegian material. *Contraception* 1989; 39: 471–5.
10. Romieu I, *et al.* Prospective study of oral contraceptive use and risk of breast cancer in women. *J Natl Cancer Inst* 1989; 81: 1313–21.
11. *UK National Case-Control Study Group.* Oral contraceptive use and breast cancer risk in young women. *Lancet* 1989; i: 973–82.
12. UK National Case-Control Study Group. Oral contraceptive use and breast cancer risk in young women: subgroup analyses. *Lancet* 1990; 335: 1507–9.
13. Kay CR, Hannaford PC. Breast cancer and the pill—a further report from the Royal College of General Practitioners' oral contraception study. *Br J Cancer* 1988; 58: 675–80.
14. CSM. Oral contraceptives and carcinoma of the breast. *Current Problems 26* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20244426&RevisionSelectionMethod=LatestReleased (accessed 14/01/08)
15. Anonymous. Cancer risks of oral contraception. *Lancet* 1989; i: 84.
16. International Committee for Research in Reproduction. Oral contraceptives and breast cancer. *JAMA* 1989; 262: 206–7.
17. CSM/MCA. Oral contraceptives and breast cancer. *Current Problems* 1998; 24: 3–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20232326&RevisionSelectionMethod=LatestReleased (accessed 14/01/08)
18. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; 347: 1713–27.
19. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. *Contraception* 1996; 54 (suppl): 1S–106S.
20. La Vecchia C, *et al.* Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 1996; 14: 260–72.
21. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; 24: 741–54.
22. Kahlenborn C, *et al.* Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. *Mayo Clin Proc* 2006; 81: 1290–1302.
23. Grabrick DM, *et al.* Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. *JAMA* 2000; 284: 1791–8.
24. Silvera SAN, *et al.* Oral contraceptive use and risk of breast cancer among women with a family history of breast cancer: a prospective cohort study. *Cancer Causes Control* 2005; 16: 1059–63.
25. Narod SA, *et al.* Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 2002; 94: 1773–9.
26. Milne RL, *et al.* Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 350–6.
27. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Breast cancer and depot-medroxyprogesterone acetate: a multinational study. *Lancet* 1991; 338: 833–8.
28. Paul C, *et al.* Depot medroxyprogesterone (Depo-Provera) and risk of breast cancer. *BMJ* 1989; 299: 759–62.
29. Skegg DCG, *et al.* Depot medroxyprogesterone acetate and breast cancer: a pooled analysis of the World Health Organization and New Zealand studies. *JAMA* 1995; 273: 799–804.
30. Shapiro S, *et al.* Risk of breast cancer in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen contraceptives. *Am J Epidemiol* 2000; 151: 396–403. Correction. *Ibid.*: 1134.

CERVIX. It is often considered difficult to carry out satisfactory epidemiological studies on the relationship between hormonal contraceptives and cervical cancer because of the many known variables that can influence the development of this type of neoplasm. For example, sexual activity *per se*, and multiple sexual partners (both of the woman and her partner) increase the risk, while the use of other non-hormonal barrier methods of contraception may offer some protection against cervical neoplasia. Nevertheless, there have been some suggestions that the use of oral contraceptives may be associated with an increased risk.

Two UK cohort studies from the 1980s revealed an increased risk of cervical cancer in women receiving oral contraceptives that was shown to increase with increasing duration of use.[1,2]

In 1992, WHO reviewed[3] these cohort data, and data from 18 case-controlled studies carried out up to 1990. They concluded that use of oral contraceptives for more than 5 years was associated with a modest increase in the relative risk of cervical squamous cell carcinoma (in the order of 1.3 to 1.8). Additional potential risk factors included recent or current use and high oestrogen dose. Of known risk factors for cervical cancer, women with multiple sexual partners, genital infection, or high parity had enhanced risks associated with oral contraceptives.[3] A later analysis[4] of 24 studies came to similar conclusions, finding a relative risk of 1.90 (95% confidence interval 1.69 to 2.13) for current use of 5 or more years. Also, the risk had returned to normal by 10 or more years after stopping hormonal contraceptive use.

Most cervical cancers are squamous cell carcinomas, but it has been proposed that oral contraceptive use might be a particular risk factor for the rarer adenocarcinoma of the cervix, the incidence of which has risen in younger women. Reviewing studies up to 1990, WHO concluded that data were insufficient to draw firm conclusions on links between oral contraceptives and the risk of cervical adenocarcinoma.[3] A case-controlled study from 1994 found an increased risk of adenocarcinoma of the cervix in users of oral contraceptives.[5] Any use of oral contraceptives was associated with an approximate doubling of risk, and use for more than 12 years was associated with a relative risk 4.4 times greater than that in women who never used an oral contraceptive. In 1996, a WHO study reported that the strength of the relationship seen for cervical adenocarcinomas and adenosquamous carcinomas and oral contraceptives was about the same as that for invasive squamous cell cervical carcinomas.[6]

Human papillomavirus (HPV) has a role in the aetiology of cervical cancer; women who are HPV positive and using oral contraceptives may be at increased risk of cervical neoplasm.[7,8] A pooled analysis of 8 case-control studies in women who tested positive for HPV DNA suggested risk of invasive squamous cervical cancer or carcinoma *in situ* was increased about threefold in those who used oral contraceptives for 5 years or more.[9] A larger systematic review,[10] which also included these 8 studies, found the increased risk for HPV positive women to be broadly similar to that for all women.

Data on the risk of cervical cancer with **progestogen-only contraceptives** are limited. WHO have investigated any possible link between the use of medroxyprogesterone acetate as a long-acting injectable contraceptive and cervical neoplasia. Analysis showed a small non-significant elevated risk (1.11; 95% confidence interval 0.9 to 1.29), and no clear association with duration of use.[11] A later case-control study[12] found no significant association between injectable progestogen contraceptives and invasive cervical cancer risk. A subsequent analysis[4] of data from 10 studies found a slightly raised risk of 1.22 (95% confidence interval 1.01 to 1.46) for women using a progestogen-only injectable contraceptive for 5 or more years, with no clear effect of time since last use.

1. Vessey MP, *et al.* Neoplasia of the cervix uteri and contraception: a possible adverse effect of the pill. *Lancet* 1983; ii: 930–4.
2. Beral V, *et al.* Oral contraceptive use, and malignancies of the genital tract: results from the Royal College of General Practitioners' oral contraception study. *Lancet* 1988; ii: 1331–5.
3. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
4. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16 573 women with cervical cancer and 35 509 women without cervical cancer from 24 epidemiological studies. *Lancet* 2007; 370: 1609–21.
5. Ursin G, *et al.* Oral contraceptive use and adenocarcinoma of cervix. *Lancet* 1994; 344: 1390–4.
6. Thomas DB, Ray RM. Oral contraceptives and invasive adenocarcinomas and adenosquamous carcinomas of the uterine cervix. *Am J Epidemiol* 1996; 144: 281–9.
7. La Vecchia C, *et al.* Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 1996; 14: 260–72.
8. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; 24: 741–54.
9. Moreno V, *et al.* Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet* 2002; 359: 1085–92.
10. Smith JS, *et al.* Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet* 2003; 361: 1159–67.
11. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer. *Contraception* 1992; 45: 299–312.
12. Shapiro S, *et al.* Risk of invasive cancer of the cervix in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen oral contraceptives (South Africa). *Cancer Causes Control* 2003; 14: 485–95.

ENDOMETRIUM. It has been shown that **combined oral contraceptives** decrease the risk of endometrial cancer. WHO analysed data from case-control and cohort studies published up to 1990,[1] including data from the large Cancer and Steroid Hormone Study (CASH) in the USA,[2] and reported that there was a highly significant trend of decreasing risk of endometrial cancer with increasing duration of use of combined oral contraceptives. The reduction in risk was estimated to be 20% after 1 year and 50% after 4 years of use.[1] The protective effect was seen for endometrial cancer with and without squamous elements,[1,2] and was found to persist for at least 15 years after cessation of use.[2] More recent studies with longer term follow-up have indicated that the protection persists for at least 20 years.[3,4] Further follow-up is required to determine the true duration of protection; data from one study[5] suggested that the reduction in risk was more pronounced in women who had stopped contraceptive use more than 25 years before, but another study[4] suggested that any protective effect may no longer be present 30 years after stopping combined oral contraceptive use.

The results of the WHO Collaborative Study on Neoplasia and Steroid Contraceptives suggested that protection may be greater with preparations containing high-dose progestogen.[6] However, another study found that risk of endometrial cancer was unrelated to progestogen potency of the oral contraceptive, although this study also reported no protective effect for less than 5 years of use.[7] Further analysis of the CASH study data[8] found that although preparations containing high and low doses of progestogen had a similar protective effect overall, it was greatest for high-dose progestogen preparations in women with a higher BMI.

Unopposed menopausal oestrogen replacement therapy is known to increase the risk of endometrial cancer (see p. 2247.3), and there is some evidence[3,7] that it reduces the protective effect of previous oral contraception.

There are limited data on the effect of **progestogen-only contraceptives** on the risk of endometrial cancer, although they would be expected to be protective. Results from the WHO Collaborative Study[9] suggest that depot medroxyprogesterone acetate reduced the risk of endometrial cancer; the estimated relative risk in users was 0.21. However, many of the women in this study received supplemental oestrogen to control menstrual irregularity, and were therefore technically taking a form of combined therapy.[10] There was some evidence that the protective effect of medroxyprogesterone acetate was greater in women who had not received oestrogen,[10] although this remains to be proven.

1. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
2. The Cancer and Steroid Hormone Study of the CDC and the National Institute of Child Health and Human Development. Combination oral contraceptive use and the risk of endometrial cancer. *JAMA* 1987; 257: 796–800.
3. Stanford JL, *et al.* Oral contraceptives and endometrial cancer: do other risk factors modify the association? *Int J Cancer* 1993; 54: 243–8.
4. Weiderpass E, *et al.* Use of oral contraceptives and endometrial cancer risk (Sweden). *Cancer Causes Control* 1999; 10: 277–84.
5. Tao MH, *et al.* Oral contraceptive and IUD use and endometrial cancer: a population-based case-control study in Shanghai, China. *Int J Cancer* 2006; 119: 2142–7.
6. Rosenblatt KA, *et al.* Hormonal content of combined oral contraceptives in relation to the reduced risk of endometrial carcinoma. *Int J Cancer* 1991; 49: 870–4.
7. Voigt LF, *et al.* Recency, duration, and progestin content of oral contraceptives in relation to the incidence of endometrial cancer. *Cancer Causes Control* 1994; 5: 227–33.
8. Maxwell GL, *et al.* Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. *Gynecol Oncol* 2006; 103: 535–40.
9. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. *Int J Cancer* 1991; 49: 186–90.
10. Szarewski A, Guillebaud J. Safety of DMPA. *Lancet* 1991; 338: 1157–8.

GASTROINTESTINAL TRACT. A link between female sex hormones and the risk of colorectal cancer has been postulated. Epidemiological studies have variously shown a possible increased risk of rectal cancer,[1] a possible decreased risk of colorectal cancer[2] in women ever having used oral contraceptives, and no association between past oral contraceptive use and colorectal cancer.[3] A meta-analysis,[4] which included these 3 studies, found a reduction in the risk of colorectal cancer for women who had ever used oral contraceptives. Duration of use was not related to risk reduction, but the effect was apparently stronger for recent contraceptive use although this was based on limited data. Subsequent studies have produced similar results. A reduction in risk has been associated with ever use of oral contraceptives in one report,[5] while others have found no effect statistically but a trend towards protection with current or recent use.[6,7] (See also under Hormone Replacement Therapy, p. 2248.1.)

1. Kune GA, *et al.* Oral contraceptive use does not protect against large bowel cancer. *Contraception* 1990; 41: 19–25.
2. Fernandez E, *et al.* Oral contraceptives, hormone replacement therapy and the risk of colorectal cancer. *Br J Cancer* 1996; 73: 1431–5.
3. Troisi R, *et al.* Reproductive factors, oral contraceptive use, and risk of colorectal cancer. *Epidemiology* 1997; 8: 75–9.
4. Fernandez E, *et al.* Oral contraceptives and colorectal cancer risk: a meta-analysis. *Br J Cancer* 2001; 84: 722–7.
5. Lin J, *et al.* Oral contraceptives, reproductive factors, and risk of colorectal cancer among women in a prospective cohort study. *Am J Epidemiol* 2007; 165: 794–801.
6. Hannaford P, Elliott A. Use of exogenous hormones by women and colorectal cancer: evidence from the Royal College of General Practitioners' Oral Contraception Study. *Contraception* 2005; 71: 95–8.
7. Nichols HB, *et al.* Oral contraceptive use, reproductive factors, and colorectal cancer risk: findings from Wisconsin. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1212–18.

LIVER. The use of **combined oral contraceptives** has been rarely associated with liver tumours, both benign (hepatic adenomas and focal nodular hyperplasia)[1] and malignant (hepatocellular carcinoma).[1,2]

Early studies of *hepatic adenoma* found that risk increased with the duration of use of oral contraceptives, and appeared to be higher in women who had used preparations with a high oestrogen content.[1] There are also case reports of adenoma that has regressed after stopping oral contraceptive use.[3] However, a study[4] in the 1990s found no increase in risk associated with contraceptive use, and the authors considered that lower doses of oestrogens might explain the different findings. The association between oral contraceptive use and *focal nodular hyperplasia* has also been

studied. One case-control study[4] found a slight increase in risk associated with use for 10 years or more. Another study[5] that followed a series of patients for about 2 years after diagnosis found no correlation between oral contraceptive use and lesion size or number, and no increase in lesion size in those patients who continued to use hormonal contraception.

Hepatocellular carcinomas are associated with hepatitis B, and are relatively common in countries where this is endemic but rare elsewhere. Case-control studies in populations at high risk for hepatocellular carcinoma suggest that the use of oral contraceptives does not significantly affect the risk, although long-term data are scanty.[6,7] However, survival after curative treatment is better in women than men, and a retrospective study from Hong Kong has suggested that this may be associated with a history of oral contraceptive use.[8] In contrast, case-control studies in countries where the prevalence of hepatitis B is low have shown an increased risk of hepatocellular carcinoma among users of oral contraceptives, particularly after long-term use (reviewed by WHO[1] and La Vecchia[2,9]). However, because the malignancy is so rare, this increased risk may be negligible.[2] For example, there has been no increase in mortality from liver cancer in young women in the UK since the introduction and use of oral contraceptives.[10] Similar findings have been reported for the USA and Sweden.[11]

There are limited data specifically on **progestogen-only contraceptives**. Results from a WHO study[12] provided no evidence that use of medroxyprogesterone acetate as a long-acting injectable contraceptive altered the risk of developing liver cancer but the power of the study to detect small alterations in risk was low.

1. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
2. La Vecchia C, *et al.* Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 1996; 14: 260–72.
3. Aseni P, *et al.* Rapid disappearance of hepatic adenoma after contraceptive withdrawal. *J Clin Gastroenterol* 2001; 33: 234–6.
4. Heinemann LAJ, *et al.* Modern oral contraceptive use and benign liver tumors: the German benign liver tumor case—control study. *Eur J Contracept Reprod Health Care* 1998; 3: 194–200.
5. Mathieu D, *et al.* Oral contraceptive use and focal nodular hyperplasia of the liver. *Gastroenterology* 2000; 118: 560–4.
6. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Combined oral contraceptives and liver cancer. *Int J Cancer* 1989; 43: 254–9.
7. Kew MC, *et al.* Contraceptive steroids as a risk factor for hepatocellular carcinoma: a case/control study in South African black women. *Hepatology* 1990; 11: 298–302.
8. Lam CM, *et al.* Better survival in female patients with hepatocellular carcinoma: oral contraceptive pills related? *J Clin Gastroenterol* 2005; 39: 533–9.
9. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; 24: 741–54.
10. Mant JWF, Vessey MP. Trends in mortality from primary liver cancer in England and Wales 1975-1992: influence of oral contraceptives. *Br J Cancer* 1995; 72: 800–3.
11. Waetjen LE, Grimes DA. Oral contraceptives and primary liver cancer: temporal trends in three countries. *Obstet Gynecol* 1996; 88: 945–9.
12. Anonymous. Depot-medroxyprogesterone acetate (DMPA) and cancer: memorandum from a WHO meeting. *Bull WHO* 1986; 64: 375–82.

OVARY. There is convincing evidence that **combined oral contraceptives** reduce the risk of ovarian cancer,[1,2] possibly as a function of their inhibition of ovulation. Relative risks for ovarian cancer have variously been reported as 0.4 to 0.8 in those who have ever used oral contraceptives, and decrease with increasing duration of use. There is evidence that there may be a delay of several years before the protective effect becomes apparent,[3] but that it persists for as long as 20 or 30 years after cessation of use.[3-5] The protective effect has been noted for both malignant and borderline malignant tumours[6] and for each of the major histological subtypes of epithelial ovarian cancer, although there have been conflicting data for mucinous tumours.[5]

It has been suggested that newer lower-dose oestrogen preparations may be slightly less protective than higher-dose preparations.[7] The relative risk for use of high-dose preparations was 0.68, and for low-dose preparations was 0.81, but it was noted that this difference could have occurred by chance. A later study[4] reported that risk reduction was not affected by oral contraceptive formulation. In contrast, another study[8] found a greater risk reduction associated with low-dose contraceptives than older high-dose preparations (odds ratio of 0.24 versus 0.70). The authors speculated that the accompanying changes in progestogen content might have played a role. This was examined using the data from the Cancer and Steroid Hormone (CASH) study, which suggested that higher progestogen potency provided greater risk reduction than lower progestogen potency, regardless of oestrogen dose.[9] Androgenicity of the progestogen does not appear to influence the protective effect of combined oral contraceptives.[10]

A systematic review[11] of 45 studies confirmed many of these findings, showing an overall relative risk of ovarian cancer of 0.73 (95% confidence interval 0.70 to 0.76) associated with ever use of oral contraceptives. Risk declined with increasing duration of use, and although the benefits were attenuated over time after stopping use, the risk of ovarian cancer was still significantly reduced 30 or more years after contraceptive use had finished. Results also suggested that changes in formulation over time had not significantly affected risk reduction.

The protective effect against ovarian cancer may have significant implications for public health. There have been substantial declines in ovarian cancer incidence and mortality in younger women in countries where oral contraceptives have become widely used; it is estimated that 3000 to 5000 cases (and consequently 2000 to 3000 deaths) are avoided each year in Europe; similar numbers are quoted in North America.[12] The number of cancers prevented each year is also likely to increase as past users age and oral contraceptive use by new users worldwide grows.[12]

There are few data on the effects of **progestogen-only contraceptives** on the risk of ovarian cancer. WHO have investigated the effect of depot medroxyprogesterone acetate on ovarian cancer, and found that it was not associated with either a decrease or increase in risk (relative risk 1.07; 95% confidence interval 0.6 to 1.8).[13] This is perhaps surprising since the preparation, like combined oral contraceptives, inhibits ovulation.

Women carrying mutations in either the BRCA1 or BRCA2 gene are at increased risk of ovarian cancer, and the effect of oral contraceptives in these women has been evaluated. Although there was no protective effect in one study,[14] others have found a risk reduction with contraceptive use similar to that reported for non-carriers.[15-18] It has been suggested that oral contraceptives might be used prophylactically to protect against ovarian cancer in women with these mutations, but this must be considered in the context of their increased risk of breast cancer (see Breast, p. 2234.2). Women with endometriosis may also be at increased risk of ovarian cancer, and an analysis[19] of the pooled data from 4 studies suggested that long-term use of oral contraceptives may also be protective in this group.

1. Whittemore AS, *et al.* Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies II: invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992; 136: 1184–1203.
2. Bosetti C, *et al.* Long-term effects of oral contraceptives on ovarian cancer risk. *Int J Cancer* 2002; 102: 262–5.
3. Rosenberg L, *et al.* A case-control study of oral contraceptive use and invasive epithelial ovarian cancer. *Am J Epidemiol* 1994; 139: 654–61.
4. Ness RB, *et al.* Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. *Am J Epidemiol* 2000; 152: 233–41.
5. Riman T, *et al.* Risk factors for invasive epithelial ovarian cancer: results from a Swedish case-control study. *Am J Epidemiol* 2002; 156: 363–73.
6. Kumle M, *et al.* Risk for invasive and borderline epithelial ovarian neoplasias following use of hormonal contraceptives: the Norwegian-Swedish Women's Lifestyle and Health Cohort Study. *Br J Cancer* 2004; 90: 1386–91.
7. Rosenblatt KA, *et al.* High-dose and low-dose combined oral contraceptives: protection against epithelial ovarian cancer and the length of the protective effect. *Eur J Cancer* 1992; 28A: 1872–6.
8. Royar J, *et al.* Low-dose oral contraceptives: protective effect on ovarian cancer risk. *Int J Cancer* 2001; 95: 370–4.
9. Schildkraut JM, *et al.* Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. *J Natl Cancer Inst* 2002; 94: 32–8.
10. Greer JB, *et al.* Androgenic progestins in oral contraceptives and the risk of epithelial ovarian cancer. *Obstet Gynecol* 2005; 105: 731–40.
11. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23 257 women with ovarian cancer and 87 303 controls. *Lancet* 2008; 371: 303–14.
12. La Vecchia C. Oral contraceptives and ovarian cancer: an update, 1998–2004. *Eur J Cancer Prev* 2006; 15: 117–24.
13. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. *Int J Cancer* 1991; 49: 191–5.
14. Modan B, *et al.* Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001; 345: 235–40.
15. Narod SA, *et al.* Oral contraceptives and the risk of hereditary ovarian cancer. *N Engl J Med* 1998; 339: 424–8.
16. McGuire V, *et al.* Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations. *Am J Epidemiol* 2004; 160: 613–18.
17. Whittemore AS, *et al.* Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. *Br J Cancer* 2004; 91: 1911–15.
18. McLaughlin JR, *et al.* Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. *Lancet Oncol* 2007; 8: 26–34.
19. Modugno F, *et al.* Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol* 2004; 191: 733–40.

SKIN. Although there have been some suggestions of a possible association between the use of oral contraceptives and the development of malignant melanoma[1-4] most studies, including analyses of relatively large numbers of women suffering from malignant melanoma, found no such association with either current or prior use of oral contraceptive preparations.[5-12] A meta-analysis of 18 case-control studies confirmed the lack of association.[13]

1. Beral V, *et al.* Malignant melanoma and oral contraceptive use among women in California. *Br J Cancer* 1977; 36: 804–9.
2. Lerner AB, *et al.* Effects of oral contraceptives and pregnancy on melanomas. *N Engl J Med* 1979; 301: 47.
3. Beral V, *et al.* Oral contraceptive use and malignant melanoma in Australia. *Br J Cancer* 1984; 50: 681–5.
4. Feskanich D, *et al.* Oral contraceptive use and risk of melanoma in premenopausal women. *Br J Cancer* 1999; 81: 918–23.
5. Bain C, *et al.* Oral contraceptive use and malignant melanoma. *J Natl Cancer Inst* 1982; 68: 537–9.
6. Helmrich SP, *et al.* Lack of an elevated risk of malignant melanoma in relation to oral contraceptive use. *J Natl Cancer Inst* 1984; 73: 617–20.
7. Green A, Bain C. Hormonal factors and melanoma in women. *Med J Aust* 1985; 142: 446–8.
8. Østerlind A, *et al.* The Danish case-control study of cutaneous malignant melanoma III: hormonal and reproductive factors in women. *Int J Cancer* 1988; 42: 821–4.
9. Palmer JR, *et al.* Oral contraceptive use and risk of cutaneous malignant melanoma. *Cancer Causes Control* 1992; 3: 547–54.
10. Holly EA, *et al.* Cutaneous melanoma in women III: reproductive factors and oral contraceptive use. *Am J Epidemiol* 1995; 141: 943–50.
11. Smith MA, *et al.* Hormonal and reproductive influences and risk of melanoma in women. *Int J Epidemiol* 1998; 27: 751–7.
12. Naldi L, *et al.* Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure, and hormonal factors: a case-control study from Italy. *Ann Epidemiol* 2005; 15: 545–50.
13. Gefeller O, *et al.* Cutaneous malignant melanoma in women and the role of oral contraceptives. *Br J Dermatol* 1998; 138: 122–4.

Ectopic pregnancy. All methods of contraception effectively reduce the risk of ectopic pregnancy overall by reducing the rate of pregnancy. However, when contraception fails the proportion of pregnancies that are ectopic is higher for users of oral and intra-uterine **progestogen-only contraceptives** and levonorgestrel implants than in the general population.[1] There is no increase in the proportion of ectopic pregnancies for methods that inhibit ovulation more reliably, such as combined oral contraceptives[1] and medroxyprogesterone acetate depot injection.[2]

A small number of cases of ectopic pregnancy after failure of **emergency contraception**, with both the Yuzpe regimen (oestrogen plus progestogen)[3] and progestogen-only contraception,[4] have been reported. However, data from clinical studies[5] and postmarketing surveillance[6] have shown that when levonorgestrel emergency contraception does rarely fail, there is no increase in the chance of ectopic pregnancy occurring.

1. Furlong L-A. Ectopic pregnancy risk when contraception fails: a review. *J Reprod Med* 2002; 47: 881–5.
2. Borgatta L, *et al.* Pregnancies diagnosed during Depo-Provera use. *Contraception* 2002; 66: 169–72.
3. Nielsen CL, Miller L. Ectopic gestation following emergency contraceptive pill administration. *Contraception* 2000; 62: 275–6.
4. Harrison-Woolrych M, Woolley J. Progestogen-only emergency contraception and ectopic pregnancy. *J Fam Plann Reprod Health Care* 2003; 29(1): 5–6.
5. Trussell J, *et al.* Ectopic pregnancy following use of progestin-only ECPs. *J Fam Plann Reprod Health Care* 2003; 29: 249.
6. Gainer E, *et al.* Progestogen-only emergency contraception. *J Fam Plann Reprod Health Care* 2003; 29(2): 60. Correction. *ibid.*: 159.

Effects on body-weight. Weight gain has been reported as an adverse effect of combined oral contraceptives, but there is no strong evidence from clinical studies to confirm that they have a significant effect on weight.[1,2] However, there is some evidence that weight gain might be associated with medroxyprogesterone acetate when given as a long-acting injectable contraceptive. There have been reports of both weight gain[3] over 5 years, and no change in weight[4] over 10 years, in women using medroxyprogesterone compared with those using a copper IUD. Studies[5,6] in adolescents using medroxyprogesterone or an oral contraceptive for 12 or 18 months have reported more weight gain in those using medroxyprogesterone, and that significant weight gain was more likely in those who were overweight when contraception was started. The risk of weight gain, however, may be confounded by several factors including age, race, diet, exercise, and prior pregnancy.

For discussion of a possible association between obesity and oral contraceptive failure, see Obesity, under Precautions, p. 2241.3.

1. Gupta S. Weight gain on the combined pill—Is it real? *Hum Reprod Update* 2000; 6: 427–31.
2. Gallo MF, *et al.* Combination contraceptives: effects on weight. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 25/09/09).
3. Bahamondes L, *et al.* Comparison of weight increase in users of depot medroxyprogesterone acetate and copper IUD up to 5 years. *Contraception* 2001; 64: 223–5.
4. Taneepanichskul S, *et al.* Effects of DMPA on weight and blood pressure in long term acceptors. *Contraception* 1999; 59: 301–3.
5. Mangan SA, *et al.* Overweight teens at increased risk for weight gain while using depot medroxyprogesterone acetate. *J Pediatr Adolesc Gynecol* 2002; 15: 79–82.
6. Bonny AE, *et al.* Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal contraceptive method. *Arch Pediatr Adolesc Med* 2006; 160: 40–5.

Effects on carbohydrate metabolism. The potential effects of oral contraceptives on carbohydrate metabolism are of concern because impaired glucose tolerance, hyperinsulinism, and insulin resistance contribute to atherogenesis and cardiovascular disease.[1] Early studies suggested that the prevalence of abnormal glucose tolerance in oral contraceptive users was increased from about 4 to 35%.[2] This decreased glucose tolerance was found to be related to oestrogen dose, particularly those greater than 75 micrograms daily, and to the type of progestogen. Marked

hyperglycaemia has been associated with contraceptives containing high doses of oestrogen but is not seen with combined oral contraceptives used currently, which contain lower doses of oestrogen.[1] Progestogens have little effect on glucose tolerance, but are associated with hyperinsulinaemia. This effect is dose-dependent, and levonorgestrel has the most potent effect, with desogestrel, gestodene, and norethisterone reported to have less effect.[1] Combined oral contraceptives can also induce insulin resistance;[1] it is believed that the oestrogen is responsible and that the progestogen modifies this effect.[3]

Despite evidence of these effects, more recent studies of lower-dose preparations containing desogestrel, levonorgestrel, or norethisterone have found little or no effect on various measurements of carbohydrate metabolism;[4-6] this lack of effect has also been confirmed in a meta-analysis[7] of studies of hormonal contraceptive use in non-diabetic women although it was noted that no strong statement could be made since few studies compared the same types of contraceptives and some had large drop out rates. Also, data from the Nurses' Health Study indicate that oral contraceptive use does not appear to increase the risk of developing type 2 diabetes mellitus.[8,9] However, a study in the USA of breast-feeding women of Hispanic origin who had recently had gestational diabetes, suggested that the use of progestogen-only, but not combined, contraceptives was associated with an increased risk of developing type 2 diabetes mellitus in this group.[10]

Injectable progestogen-only contraceptives have been reported in epidemiological studies to be associated with an increase in the incidence of type 2 diabetes mellitus. However, metabolic studies in lean, non-diabetic women have generally found no effect on glucose concentrations, suggesting that obesity or weight gain associated with injectable progestogen-only contraceptive use may play a role.[11]

1. Crook D, Godsland I. Safety evaluation of modern oral contraceptives: effects on lipoprotein and carbohydrate metabolism. *Contraception* 1998; 57: 189–201.
2. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; (Oct.): 659–62.
3. Godsland IF, *et al.* Insulin resistance, secretion, and metabolism in users of oral contraceptives. *J Clin Endocrinol Metab* 1992; 74: 64–70.
4. Kim C, *et al.* Oral contraceptive use and association with glucose, insulin, and diabetes in young adult women: the CARDIA study. *Diabetes Care* 2002; 25: 1027–32.
5. Troisi RJ, *et al.* Oral contraceptive use and glucose metabolism in a national sample of women in the United States. *Am J Obstet Gynecol* 2000; 183: 389–95.
6. Knopp RH, *et al.* Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception* 2001; 63: 1–11.
7. Lopez LM, *et al.* Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. Available in The Cochrane Database of Systematic Reviews: Issue 4, Chichester: John Wiley; 2009 (accessed 21/07/10).
8. Rimm EB, *et al.* Oral contraceptive use and the risk of type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. *Diabetologia* 1992; 35: 967–72.
9. Chasan-Taber L, *et al.* A prospective study of oral contraceptives and NIDDM among US women. *Diabetes Care* 1997; 20: 330–5.
10. Kjos SL, *et al.* Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. *JAMA* 1998; 280: 533–8.
11. Kahn HS, *et al.* Effects of injectable or implantable progestin-only contraceptives on insulin-glucose metabolism and diabetes risk. *Diabetes Care* 2003; 26: 216–25.

Effects on the cardiovascular system. Soon after their introduction in the 1960s it became apparent that **combined oral contraceptives** were associated with an increased risk of cardiovascular effects including *hypertension, venous thromboembolism, myocardial infarction,* and *stroke.* Consequently, there are contra-indications and precautions relating to their use in women with risk factors for cardiovascular disease (see under Precautions, p. 2241.2).

Changing patterns of use, and a progressive reduction in doses, have meant a continued need to evaluate the risks associated with oral contraceptives.

Current use of lower-dose combined oral contraceptives (less than 50 micrograms oestrogen) increases blood pressure in many women, and also results in a small but significant increased risk of venous thromboembolism. Any increased risk of myocardial infarction and stroke is low in women aged less than 35 years who do not smoke and who do not have pre-existing hypertension. Further details of these adverse effects are covered in the sections below.

The effect of progestogens on the cardiovascular risk profile of oral contraceptives has not been established. Some of the newer progestogens have been reported to have more favourable effects on plasma lipids (see Effects on Lipids, p. 2239.2) and there is some suggestion that they may have a lower risk of myocardial infarction, but there are insufficient data to confirm or refute this. However, it has been reported that desogestrel and gestodene are associated with a higher risk of venous thromboembolism than older progestogens.

The Nurses' Health Study found no association between ever having used oral contraceptives and death from cardiovascular disease.[1] The Royal College of General Practitioners' study reported an increase in death from cerebrovascular disease with current or recent (within 10 years) use of oral contraceptives, but not for past use (greater than 10 years).[2]

Some general reviews are cited below.[3-7]

1. Colditz GA, *et al.* Oral contraceptive use and mortality during 12 years of follow-up: the Nurses' Health Study. *Ann Intern Med* 1994; 120: 821–6.
2. Beral V, *et al.* Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *BMJ* 1999; 318: 96–100.
3. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptive: summary of conclusions. *Wkly Epidem Rec* 1997; 72: 361–3.
4. Chasan-Taber L, Stampfer MJ. Epidemiology of oral contraceptives and cardiovascular disease. *Ann Intern Med* 1998; 128: 467–77.
5. WHO. Cardiovascular disease and steroid hormone contraception. *WHO Tech Rep Ser 877* 1998. Also available at: http://libdoc.who.int/trs/WHO_TRS_877.pdf (accessed 14/01/08)
6. Hannaford P. Cardiovascular events associated with different combined oral contraceptives: a review of current data. *Drug Safety* 2000; 22: 361–71.
7. Godsland IF, *et al.* Occlusive vascular diseases in oral contraceptive users: epidemiology, pathology and mechanisms. *Drugs* 2000; 60: 721–869.

HYPERTENSION. In a one-year prospective multicentre study[1] involving 704 women under the age of 35 using a **combined oral contraceptive** containing levonorgestrel 250 micrograms and ethinylestradiol 50 micrograms and 703 women using a non-hormonal intra-uterine contraceptive device, those using the oral contraceptive developed higher systolic and diastolic blood pressures (systolic pressures were 3.6 to 5.0 mmHg higher, diastolic pressures were 1.9 to 2.7 mmHg higher). Only 4 women receiving oral contraceptives developed hypertension. A similar increase in blood pressure was noted in a study[2] involving 222 users of combined oral contraceptives containing 30 micrograms ethinylestradiol. There was a greater increase in blood pressure for those preparations containing 250 micrograms levonorgestrel than those containing 150 micrograms levonorgestrel.

More recently, data from the Nurses' Health Study[3] showed an increased risk (relative risk 1.8) for the development of hypertension in women taking lower-dose combined oral contraceptives. Increasing doses of progestogen were positively associated with hypertension, and the lowest risk occurred in women receiving triphasic preparations, which have the lowest total dose of progestogen. A UK study[4] found a small increase in blood pressure of 2.3/1.6 mmHg associated with the use of combined oral contraceptives. In this study, oral **progestogen-only contraceptives** were not associated with an increase in blood pressure. A more recent review[5] also found no evidence that use of progestogen-only contraception for up to 2 to 3 years was associated with high blood pressure. Similarly, depot medroxyprogesterone acetate does not raise blood pressure.[6]

1. WHO Task Force on Oral Contraceptives. The WHO multicentre trial of the vasopressor effects of combined oral contraceptives 1: comparisons with IUD. *Contraception* 1989; 40: 129–45.
2. Khaw K-T, Peart WS. Blood pressure and contraceptive use. *BMJ* 1982; 285: 403–7.
3. Chasan-Taber L, *et al.* Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation* 1996; 94: 483–9.
4. Dong W, *et al.* Blood pressure in women using oral contraceptives: results from the Health Survey for England 1994. *J Hypertens* 1997; 15: 1063–8.
5. Hussain SF. Progestogen-only pills and high blood pressure: is there an association? A literature review. *Contraception* 2004; 69: 89–97.
6. Taneepanichskul S, *et al.* Effects of DMPA on weight and blood pressure in long term acceptors. *Contraception* 1999; 59: 301–3.

MYOCARDIAL INFARCTION. Case-control studies from the 1970s and early 1980s revealed an increased risk of acute myocardial infarction in users of oral contraceptives (generally of the high-dose type) relative to those never having used them.[1,2] Several large cohort studies have provided similar findings.[3-6] Among current users the reported[1-3,5,6] relative risk of myocardial infarction has varied between about 1.8 and 6.4, whereas in women having used oral contraceptives in the past the reported[2-5] relative risk has varied between about 0.8 and 2.5. Women who *smoke* while using oral contraceptives are at a greatly increased risk,[1,3,7] those smoking more than 15 to 25 cigarettes daily having at least a twentyfold increased risk of myocardial infarction compared with non-smoking non-oral contraceptive users.[1,3]

These studies have principally been from the USA or the UK. The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception has reported the findings of an international multicentre case-control study.[8] The overall odds ratio for acute myocardial infarction in current users of combined oral contraceptives was 5.01 in Europe and 4.78 in Africa, Asia, and Latin America. This increase in risk reflected use in women who had coexistent risk factors such as smoking, and who had not had their blood pressure checked before use. Thus, when the background incidence of acute myocardial infarction is taken into account, use of combined oral contraceptives in non-smoking women aged less than 35 years is associated with an excess of 3 per million women-years, and this is likely to be lower in those women who have their blood pressure screened before and during use. However, in older women who smoke, the excess risk associated with the use of combined oral contraceptives is substantial (400 per million women-years). There was no increase in risk associated with past use of oral contraceptives irrespective of duration of use.

There has been interest in the effect of different progestogen components on the risk of myocardial infarction. Limited data from the WHO study[8] and from the USA[9] and the UK[10] suggested no difference in risk between desogestrel or gestodene compared with levonorgestrel. Analysis of European data[11] suggested a reduction in risk with gestodene- and desogestrel-containing products compared with other progestogens (0.28; 95% confidence intervals 0.09 to 0.86). A WHO Scientific Group meeting concluded that available data did not allow the conclusion that risk of myocardial infarction was related to progestogen type.[12]

More recently, data on combined oral contraceptives that have lower oestrogen doses have revealed at most small and non-significant increases in risk of acute myocardial infarction associated with oral contraceptive use,[10,13-15] although case-control studies have suggested that again, there may be a greatly increased risk in women who smoke more than 20 to 25 cigarettes daily.[10,16] However, subsequent meta-analyses including these and other studies have concluded that, overall, there was an increased risk of myocardial infarction with current use of lower-dose combined oral contraceptives (oestrogen less than 50 micrograms). Subgroup analyses of progestogen type found that there was an increased risk in users of second generation contraceptives (generally containing levonorgestrel) compared with non-users; calculated odds ratios were 2.18 (1.62 to 2.94),[17] 2.17 (1.76 to 2.69),[18] and 1.85 (1.03 to 3.32).[19] However, the risk was not increased in users of third generation contraceptives (generally containing desogestrel or gestodene) compared with non-users.[17-19] Clinically, although the risk of myocardial infarction may be increased, the absolute risk is very low in healthy young women who do not smoke and do not have cardiovascular risk factors. Despite reassuring data for these newer progestogens regarding the risk of myocardial infarction, there is probably an increased risk of venous thromboembolism associated with desogestrel or gestodene (see p. 2238.1).

1. Shapiro S, *et al.* Oral-contraceptive use in relation to myocardial infarction. *Lancet* 1979; i: 743–7.
2. Slone D, *et al.* Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. *N Engl J Med* 1981; 305: 420–4.
3. Royal College of General Practitioners' Oral Contraception Study. Further analyses of mortality in oral contraceptive users. *Lancet* 1981; i: 541–6.
4. Stampfer MJ, *et al.* A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases. *N Engl J Med* 1988; 319: 1313–17.
5. Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. *BMJ* 1989; 298: 165–8.
6. Vessey MP, *et al.* Mortality among oral contraceptive users: 20 year follow up of women in a cohort study. *BMJ* 1989; 299: 1487–91.
7. Goldbaum GM, *et al.* The relative impact of smoking and oral contraceptive use on women in the United States. *JAMA* 1987; 258: 1339–42.
8. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. *Lancet* 1997; 349: 1202–9.
9. Jick H, *et al.* Risk of acute myocardial infarction and low-dose combined oral contraceptives. *Lancet* 1996; 347: 627–8.
10. Dunn N, *et al.* Oral contraceptives and myocardial infarction: results of the MICA case-control study. *BMJ* 1999; 318: 1579–83.
11. Lewis MA, *et al.* The use of oral contraceptives and the occurrence of acute myocardial infarction in young women: results from the transnational study on oral contraceptives and the health of young women. *Contraception* 1997; 56: 129–40.
12. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives: summary of conclusions. *Wkly Epidem Rec* 1997; 72: 361–3.
13. Thorogood M, *et al.* Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case-control study. *Br J Obstet Gynaecol* 1991; 98: 1245–53.
14. Sidney S, *et al.* Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. *Circulation* 1998; 98: 1058–63.
15. Tanis BC, *et al.* Oral contraceptives and the risk of myocardial infarction. *N Engl J Med* 2001; 345: 1787–93.
16. Rosenberg L, *et al.* Low-dose oral contraceptive use and the risk of myocardial infarction. *Arch Intern Med* 2001; 161: 1065–70.
17. Spitzer WO, *et al.* Myocardial infarction and third generation oral contraceptives: aggregation of recent studies. *Hum Reprod* 2002; 17: 2307–14.
18. Khader YS, *et al.* Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. *Contraception* 2003; 68: 11–17.
19. Baillargeon J-P, *et al.* Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005; 90: 3863–70.

STROKE. Current use of **combined oral contraceptives** has been associated with an increased risk of stroke, with most data relating to older high-dose oestrogen preparations. In general this association has been strongest for ischaemic stroke, and relatively weak for haemorrhagic stroke.[1] A Danish study found that lower-dose oral contraceptives (30 to 40 micrograms of oestrogen) were associated with a lower risk of cerebral thromboembolism than preparations containing 50 micrograms oestrogen.[2]

Data on 2198 cases of stroke (haemorrhagic, ischaemic, and unclassified) and 6086 controls have been reported from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception.[3,4] For all strokes combined, odds ratios for the current use of lower-dose (less than 50 micrograms oestrogen) and higher-dose preparations were, respectively, 1.41 (95% confidence intervals 0.90 to 2.20) and 2.71 (1.70 to 4.32) in Europe, and 1.86 (1.49 to 2.33) and 1.92 (1.48 to 2.50) in Africa, Asia, and Latin America. In Europe, it was estimated that the incidence rate of stroke in women aged 20 to 44 years was 4.8 per 100 000 women-years, and that this was increased to 6.7 per 100 000 in users of lower-dose preparations and 12.9 per 100 000 in users of higher-dose preparations.[3]

The risk of haemorrhagic stroke was significant only in women aged greater than 35 years, those who had a history of hypertension, and those who were current smokers.[3]

The overall odds ratio for ischaemic stroke was 2.99 (1.65 to 5.40) in Europe and 2.93 (2.15 to 4.00) in Africa, Asia, and Latin America.[4] Odds ratios were lower in women aged less than 35 years, those who did not smoke, those with no history of hypertension, and those who reported that their blood pressure had been checked before use. Duration of current use and past use were unrelated to risk.[4] A similar overall odds ratio of 2.3 (1.15 to 4.59) has been reported from the UK.[5] Similar findings have also been published from the USA.[6] Lower-dose preparations (less than 50 micrograms oestrogen) were associated with a non-significant increase in ischaemic stroke; the odds ratio was 1.18 (0.54 to 2.59); a later meta-analysis considered the association between lower-dose combined oral contraceptives and stroke to be tenuous at best, and possibly non-existent.[7]

A meta-analysis[8] of studies of ischaemic stroke found that there was an overall increased risk associated with the current use of oral contraceptives. However, the risk was less elevated with lower oestrogen doses, and in studies that controlled for smoking and hypertension.

As regards the effect of the type of progestogen on risk of stroke, one case-control study[9] reported that there was no significant difference in risk of ischaemic stroke between lower-dose oral contraceptives containing second generation progestogens and those containing desogestrel, gestodene, or norgestimate. However, another study[10,11] found that levonorgestrel- or norgestimate-containing preparations were associated with a higher risk of cerebral thrombosis than preparations containing desogestrel or gestodene. A re-analysis of the WHO data led to the cautious conclusion that the risk for stroke between second and third generation progestogens was similar,[12] and this was also supported by analysis of the General Practice Research Database[13] and a Dutch case-control study.[14] Meta-analyses[8,15] also found no significant difference between progestogen generations in the risk of ischaemic stroke.

Data for **progestogen-only contraceptives** are limited. The Danish study reported no increase in cerebral thromboembolic attacks in users of oral progestogen-only contraceptives; the odds ratio was 0.9 (0.4 to 2.4).[2]

1. Vessey MP, *et al.* Oral contraceptives and stroke: findings in a large prospective study. *BMJ* 1984; **289:** 530–1.
2. Lidegaard Ø. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. *BMJ* 1993; **306:** 956–63.
3. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 1996; **348:** 505–10.
4. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 1996; **348:** 498–505.
5. Nightingale AL, Farmer RDT. Ischemic stroke in young women: a nested case-control study using the UK General Practice Research Database. *Stroke* 2004; **35:** 1574–8.
6. Petitti DB, *et al.* Stroke in users of low-dose oral contraceptives. *N Engl J Med* 1996; **335:** 8–15.
7. Chan W-S, *et al.* Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med* 2004; **164:** 741–7.
8. Gillum LA, *et al.* Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA* 2000; **284:** 72–8.
9. Heinemann LAJ, *et al.* Case-control study of oral contraceptives and risk of thromboembolic stroke: results from international study on oral contraceptives and health of young women. *BMJ* 1997; **315:** 1502–4.
10. Lidegaard Ø, Kreiner S. Cerebral thrombosis and oral contraceptives: a case-control study. *Contraception* 1998; **57:** 303–14.
11. Lidegaard Ø. Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. *Contraception* 2002; **65:** 197–205.
12. Poulter NR, *et al.* Effect on stroke of different progestagens in low oestrogen dose oral contraceptives. *Lancet* 1999; **354:** 301–2.
13. Jick SS, *et al.* Risk of idiopathic cerebral haemorrhage in women on oral contraceptives with differing progestagen components. *Lancet* 1999; **354:** 302–3.
14. Kemmeren JM, *et al.* Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. *Stroke* 2002; **33:** 1202–8.
15. Baillargeon J-P, *et al.* Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 3863–70.

VENOUS THROMBOEMBOLISM. Use of **combined oral contraceptives** has long been known to be associated with an increased risk of venous thromboembolic events, particularly deep-vein thrombosis and pulmonary embolism. This increased risk applies both to idiopathic events and events associated with surgery or trauma, is limited to current users and is probably highest in the first year of use. Most early data relate to high-dose combined preparations, and it has been suggested by some studies,[1] but not others,[2,3] that preparations containing lower doses of oestrogen may be associated with a lower risk. More recently, reports have identified an increased risk of cerebral-vein thrombosis with oral contraceptives.[4]

The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception reported data from over 10 times more cases than any previous study.[5] The increased risk of idiopathic deep-vein thrombosis and/or pulmonary embolism associated with current use of combined oral contraceptives was 4.15 (95% confidence intervals 3.09 to 5.57) in Europe and 3.25 (2.59 to 4.08) in Africa, Asia, and Latin America. The increased risk was apparent within 4 months of starting use, was unaffected by duration of use, and had disappeared within 3 months of stopping use. Risk was unaffected by age, hypertension, or smoking (in contrast to myocardial infarction, see p. 2237.2), but was increased in those with a body-mass index greater than 25 kg/m^2 and in those with a history of hypertension of pregnancy. Of preparations containing progestogens of the norethisterone or norgestrel type, risk was non-significantly less with lower-dose oestrogen than with high-dose oestrogen.

The progestogen component has generally been considered to be unrelated to thromboembolic events; therefore, it came as a surprise when WHO found a higher risk in combined oral contraceptives containing *desogestrel* or *gestodene* than in those containing older progestogens.[5] These risk data were the subject of a separate report,[6] and were subsequently confirmed by 3 further case-control studies.[7-9] The increased risk varied from 4.8 to 9.1 compared with non-users, and was found to be 1.5 to 2.6 times higher than for preparations containing levonorgestrel or other progestogens. The incidence of venous thromboembolic disease has been estimated to be 25 per 100 000 users per year for desogestrel- and gestodene-containing products and 15 per 100 000 users per year for products containing low-dose oestrogen with other progestogens, compared with 5 per 100 000 per year for non-users. The risk was especially high in women with the factor V Leiden mutation,[8] who are at increased risk of thrombosis, but screening to exclude these women from using oral contraceptives was not considered necessary.[10,11] Despite much debate about possible bias and confounding in these results,[12,13] and the ambiguous or contradictory results of subsequent studies,[14-16] many sources seem now to agree with the 1997 conclusion of a WHO scientific group meeting[17] that there is a modestly increased risk of venous thromboembolism associated with the use of products containing desogestrel or gestodene, compared with levonorgestrel. The extent of any risk associated with combined products containing *drospirenone* has also been questioned. Data from a prescription event monitoring study suggested that it was associated with a high incidence of deep-vein thrombosis and pulmonary embolism,[18] but the authors acknowledged potential bias that may have affected the result. Subsequent large cohort studies[19,20] reported that the risk of venous thromboembolism was similar to that for users of other combined oral contraceptives, including levonorgestrel-containing preparations. Products containing *cyproterone* are also associated with increased risk (see Effects on the Cardiovascular System, under Cyproterone Acetate, p. 2262.3).

Regulatory agencies have reacted in different ways to these data. The UK CSM has advised caution in prescribing of these products (see Cardiovascular Disease under Precautions, p. 2241.2), as have some other European authorities.

The mechanism behind differences in thrombotic potential is unknown, but there is evidence that oral contraceptives may increase concentrations of prothrombin and factor VIII, and induce a resistance to the blood's natural anticoagulation system.[11] These effects may be greater with products containing desogestrel and gestodene compared with older progestogens.[11] Thrombophilias, including factor V Leiden, further increase the risk of thromboembolism from hormonal contraceptives.[21]

There has also been some concern about a possible increase in cardiovascular risk with a **transdermal patch** that releases ethinylestradiol and norelgestromin, because users are exposed to about 60% more total oestrogen than users of an oral contraceptive containing ethinylestradiol 35 micrograms (peak serum concentrations are lower but steady-state concentrations are higher). However, 2 studies comparing the patch with a combined oral contraceptive (ethinylestradiol plus norgestimate) came to different conclusions; one found the risk of venous thromboembolism to be similar,[22] while the other found a twofold increase in risk with the patch.[23] Further study is needed to explain this discrepancy, and to determine whether there is any effect on the risks of myocardial infarction and stroke.

1. Vessey M, *et al.* Oral contraceptives and venous thromboembolism: findings in a large prospective study. *BMJ* 1986; **292:** 526.
2. Kierkegaard A. Deep vein thrombosis and the oestrogen content in oral contraceptives—an epidemiological analysis. *Contraception* 1985; **31:** 29–41.
3. Helmrich SP, *et al.* Venous thromboembolism in relation to oral contraceptive use. *Obstet Gynecol* 1987; **69:** 91–5.
4. Dentali F, *et al.* Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. *Blood* 2006; **107:** 2766–73.
5. WHO Collaborative Study Group. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995; **346:** 1575–82.
6. WHO Collaborative Study Group. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. *Lancet* 1995; **346:** 1582–8.
7. Jick H, *et al.* Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; **346:** 1589–93.
8. Bloemenkamp KWM, *et al.* Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. *Lancet* 1995; **346:** 1593–6.
9. Spitzer WO, *et al.* Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996; **312:** 83–8.
10. Vandenbroucke JP, *et al.* Factor V Leiden: should we screen oral contraceptive users and pregnant women? *BMJ* 1996; **313:** 1127–30.
11. Vandenbroucke JP, *et al.* Oral contraceptives and the risk of venous thrombosis. *N Engl J Med* 2001; **344:** 1527–35.
12. Lewis MA, *et al.* The increased risk of venous thromboembolism and the use of third generation progestagens: role of bias in observational research. *Contraception* 1996; **54:** 5–13.
13. Farley TMM, *et al.* Oral contraceptives and thrombotic diseases: impact of new epidemiologic studies. *Contraception* 1996; **54:** 193–5.
14. Farmer RDT, *et al.* Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet* 1997; **349:** 83–8.
15. Farmer RDT, *et al.* Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of General Practice Research Database. *BMJ* 2000; **321:** 477–9.
16. Jick H, *et al.* Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000; **321:** 1190–5. Correction. *ibid.* 2001; **322:** 28.
17. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives: summary of conclusions. *Wkly Epidem Rec* 1997; **72:** 361–3.
18. Pearce HM, *et al.* Deep vein thrombosis and pulmonary embolism reported in the Prescription Event Monitoring Study of Yasmin. *Br J Clin Pharmacol* 2005; **60:** 98–102.
19. Dinger JC, *et al.* The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. *Contraception* 2007; **75:** 344–54.
20. Seeger JD, *et al.* Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007; **110:** 587–93.
21. Wu O, *et al.* Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost* 2005; **94:** 17–25.
22. Jick SS, *et al.* Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 micrograms of ethinyl estradiol. *Contraception* 2006; **73:** 223–8.
23. Cole JA, *et al.* Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol* 2007; **109:** 339–46.

Effects on the ears. In the Royal College of General Practitioners' study of oral contraception in the UK,[1] by 1981 there had been 13 cases of newly occurring otosclerosis in each of the groups of oral contraceptive users (101 985 woman-years) and controls (146 534 woman-years); this showed a non-significant relative risk of 1.29. Although, by analogy with pregnancy, it may be prudent to suppose that oral contraceptives could exacerbate pre-existing otosclerosis, the data do not support the view that the condition is associated with their use. Similarly, the Oxford Family Planning Association contraceptive study[2] of 17 032 women followed for up to 26 years found no association between oral contraceptive use and the development of a range of ear diseases, including otosclerosis.

1. Kay CR, Wingrave SJ. Oral contraceptives and otosclerosis. *BMJ* 1984; **288:** 1164.
2. Vessey M, Painter R. Oral contraception and ear disease: findings in a large cohort study. *Contraception* 2001; **63:** 61–3.

Effects on the eyes. Analysis of data from 2 large UK cohort studies suggested that oral contraceptive use does not increase the risk of eye disease, with the possible exception of retinal vascular lesions.[1] Retinal vein thrombosis has also been reported after the use of emergency contraception.[2] The patient presented with a 10-day history of blurred vision that started the day after taking a regimen of ethinylestradiol with norgestrel; the condition resolved after 2 months of treatment with low-dose aspirin.

1. Vessey MP, *et al.* Oral contraception and eye disease: findings in two large cohort studies. *Br J Ophthalmol* 1998; **82:** 538–42.
2. Lake SR, Vernon SA. Emergency contraception and retinal vein thrombosis. *Br J Ophthalmol* 1999; **83:** 630–1.

Effects on fertility. After stopping hormonal contraceptives some patients may develop amenorrhoea, anovulation, and infertility. This infertility, however, has been shown by most studies to be only temporary.

Data from the Oxford Family Planning Association study[1] have indicated that impairment of fertility after oral contraceptives was only very slight and short-lived in women who had previously had a baby. In nulliparous women aged 25 to 29 years impairment of fertility was more pronounced but the effect had almost entirely disappeared after 48 months. In nulliparous women aged 30 to 34 years the duration of impairment was longer but, again, this was not permanent as by 72 months after stopping oral contraceptive use the numbers of women who had not conceived were similar to a group who had previously used non-hormonal methods of contraception. In contrast to women using intra-uterine devices, in whom long-term use was associated with greater impairment of fertility than short-term (less than 42 months) use, there appears to be no association between fertility and duration of oral contraceptive use.[2] However, a later survey,[3] although concurring that the effects were transient, did find a relationship between duration of use of combined oral contraceptives and subsequent time to pregnancy.

Oral progestogen-only preparations do not appear to have a significant effect on fertility.[3] Smaller studies have also indicated that injectable progestogen-only contraceptives have no long-lasting effects on fertility;[3,4] but it has been suggested that a return to ovulation occurs significantly earlier in prior norethisterone enantate users than in medroxyprogesterone users.[5]

Infertility may also be related to the presence of pelvic inflammatory disease; for further details concerning the role of oral contraceptives in this disorder, see Pelvic Inflammatory Disease, p. 2240.3.

1. Anonymous. "Pill" use appears to impair fertility in a certain group of women. *Pharm J* 1986; 236: 227.
2. Doll H, *et al.* Return of fertility in nulliparous women after discontinuation of the intrauterine device: comparison with women discontinuing other methods of contraception. *Br J Obstet Gynaecol* 2001; 108: 304–14.
3. Hassan MAM, Killick SR. Is previous use of hormonal contraception associated with a detrimental effect on subsequent fecundity? *Hum Reprod* 2004; 19: 344–51.
4. Potterby K, *et al.* Return of ovulation and fertility in women using norethisterone enanthate. *Contraception* 1984; 29: 447–55.
5. Garza-Flores J, *et al.* Return to ovulation following the use of long-acting injectable contraceptives: a comparative study. *Contraception* 1985; 31: 361–6.

Effects on the gallbladder. Data from the Royal College of General Practitioners' (RCGP) oral contraception study accumulated up to December 1979 revealed no overall increased risk of gallbladder disease in the long-term, despite the indications of earlier data and other studies relating to short-term use.[1] Further studies[2,3] have identified an increased risk of gallbladder disease in oral contraceptive users under the age of 30 or 20, respectively. A systematic review[4] also found that oral contraceptives were associated with a slightly and transiently increased risk of gallbladder disease. However, the results of separate studies varied considerably and the reviewers highlighted several possible confounding factors and biases, nonetheless, it was concluded that newer lower-dose contraceptives (less than 50 micrograms of oestrogen) were less likely to cause problems than older formulations. Later data from the RCGP study showed an increase in risk of mild hepatitis during the first 4 years of oral contraceptive use, possibly reflecting gallstone-associated cholestasis.[5] This risk then decreased to less than that seen in women who had never used oral contraceptives.

1. Wingrave SJ, Kay CR. Oral contraceptives and gallbladder disease: Royal College of General Practitioners' oral contraception study. *Lancet* 1982; II: 957–9.
2. Scragg RKR, *et al.* Oral contraceptives, pregnancy, and endogenous oestrogen in gall stone disease—a case-control study. *BMJ* 1984; 288: 1795–9.
3. Strum BL, *et al.* Oral contraceptives and other risk factors for gallbladder disease. *Clin Pharmacol Ther* 1986; 39: 335–41.
4. Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. *Am J Public Health* 1993; 83: 1113–20.
5. Hannaford PC, *et al.* Combined oral contraceptives and liver disease. *Contraception* 1997; 55: 145–51.

Effects on the gastrointestinal tract. Several studies,[1-3] epidemiological data,[4] and a meta-analysis,[5] have shown a weak association between oral contraceptive use and the onset of Crohn's disease or ulcerative colitis. However, the suggestion that oral contraceptives have an aetiological role in chronic inflammatory bowel disease cannot be regarded as established.

The rate of relapse of Crohn's disease in women taking oral contraceptives has also been studied. Although one study[6] reported an increased risk of relapse in women who had taken oral contraceptives in the past, both this study and another prospective cohort study[7] found no increase in risk in current users. These results may have been influenced by smoking, or changes in oestrogen dose and progestogen content.

Women with inflammatory bowel disease may be offered the same contraceptive choices as other women, although oral contraceptive absorption, and hence efficacy, may be reduced when there is small bowel involvement or malabsorption.[8]

1. Correa G, *et al.* Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. *Int J Epidemiol* 1998; 27: 397–404.
2. Sicilia B, *et al.* Environmental risk factors and Crohn's disease: a population-based, case-control study in Spain. *Dig Liver Dis* 2001; 33: 762–7.
3. García Rodríguez LA, *et al.* Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther* 2005; 22: 309–15.
4. Alic M. Epidemiology supports oral contraceptives as a risk factor in Crohn's disease. *Gut* 2000; 46: 140.
5. Godet PG, *et al.* Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. *Gut* 1995; 37: 668–73.
6. Timmer A, *et al.* Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. *Gastroenterology* 1998; 114: 1143–50.
7. Cornes J, *et al.* Oral contraceptive use and the clinical course of Crohn's disease: a prospective cohort study. *Gut* 1999; 45: 218–22.
8. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Clinical guidance: sexual and reproductive health for individuals with inflammatory bowel disease (issued June 2009). Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceIBD09.pdf (accessed 25/09/09)

Effects on lipids. Combined oral contraceptives have been reported to be associated with an excess risk of various adverse cardiovascular events (see p. 2237.1). Because other epidemiological evidence suggests that the composition of blood lipids may be one of several factors involved in the aetiology of some of these disorders, many workers have investigated the biochemical profiles of women taking various formulations of oral contraceptives. Results have often been conflicting as the net effect is the result of opposing actions of the oestrogen and the progestogen components, and depends on the ratio between these. In general, the oestrogen component increases triglycerides, but decreases low-density lipoproteins, whereas the progestogen component tends to decrease high-density lipoproteins and increase low-density lipoproteins, particularly if it is androgenic (19-nortestosterone-derived progestogens). Newer non-androgenic progestogens such as desogestrel and gestodene appear to have a less detrimental effect on serum lipids. However, the contribution of these lipid changes to the incidence of cardiovascular disease in oral contraceptive users is uncertain. In particular, contrary to expectations, desogestrel and gestodene appear to be associated with a higher risk of venous thromboembolism than older progestogens (see p. 2238.1).

Some references to the effects of various oral contraceptives on serum lipid profiles are given below.[1-4]

For further details concerning the proposed role of the various serum lipids and subfractions in the aetiology of cardiovascular disease, see Hyperlipidaemias, p. 1248.1.

For reports of pancreatitis secondary to hyperlipidaemia associated with the use of combined oral contraceptives, see p. 2240.2.

1. Crook D, Godsland I. Safety evaluation of modern oral contraceptives: effects on lipoprotein and carbohydrate metabolism. *Contraception* 1998; 57: 189–201. Correction. *ibid.*: 420.
2. Knopp RH, *et al.* Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception* 2001; 63: 1–11.
3. Graff-Iversen S, Tonstad S. Use of progestogen-only contraceptives/medications and lipid parameters in women age 40 to 42 years: results of a population-based cross-sectional Norwegian Survey. *Contraception* 2002; 66: 7–13.
4. Gaspard U, *et al.* A randomized study on the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on lipid and lipoprotein metabolism over a period of 13 cycles. *Contraception* 2004; 69: 271–8.

Effects on the liver. The use of combined oral contraceptives has been rarely associated with the benign liver tumours, hepatic adenoma and focal nodular hyperplasia (see under Carcinogenicity, p. 2235.3).

Hepatitis possibly associated with gallstones has also been reported (see Effects on the Gallbladder, above).

Effects on mental state. Changes in mood and affect have been reported with oral contraceptives, and the onset of depression is a common reason given for stopping use. Nonetheless, a review[1] concluded that most women taking oral contraceptives actually feel beneficial effects, with less variability in affect across the menstrual cycle and less negative affect during the menstrual phase compared with non-users. However, there may be a subgroup of women predisposed to negative changes in mood and affect because of factors such as a history of depression, premenstrual mood symptoms before oral contraceptive use, a history of mood symptoms related to pregnancy, or a family history of mood complaints related to oral contraceptives. A lower ratio of progestogen to oestrogen was associated with more negative mood changes in women with a history of premenstrual emotional symptoms, while a higher ratio was associated with negative changes in women without such a history. In addition, monophasic regimens appeared to have a greater stabilising effect than triphasic preparations. Some possible mechanisms have been suggested to explain how combined hormonal contraceptives might influence mood.[2]

Cohort studies of injectable[3] and implantable[4] progestogen-only contraceptives found no overall change in depressive symptom score. A small increase in depressive score noted at the 2-year follow-up of implant users was found to occur in women who also had a decrease in relationship satisfaction, which the authors concluded was independent of contraceptive use. Another study[5] found an association between injectable medroxyprogesterone acetate and depressive symptoms, but other factors that might have influenced this result were also identified and another explanation could not be ruled out.

1. Oinonen KA, Mazmanian D. To what extent do oral contraceptives influence mood and affect? *J Affect Disord* 2002; 70: 229–40.
2. Kurshan N, Epperson CN. Oral contraceptives and mood in women with and without premenstrual dysphoria: a theoretical model. *Arch Womens Ment Health* 2006; 9: 1–14.
3. Westhoff C, *et al.* Depressive symptoms and Depo-Provera. *Contraception* 1998; 57: 237–40.
4. Westhoff C, *et al.* Depressive symptoms and Norplant contraceptive implants. *Contraception* 1998; 57: 241–5.
5. Civic D, *et al.* Depressive symptoms in users and non-users of depot medroxyprogesterone acetate. *Contraception* 2000; 61: 385–90.

Effects on the musculoskeletal system. *BONE DENSITY.* Combined oral contraceptives are generally considered not to have a detrimental effect on bone mineral density but study results have been inconsistent and any clinical significance unclear. However, overall, combined oral contraceptives appear not to affect bone mineral density or biochemical markers of bone turnover.[1]

Reviews of studies in different age groups have found that bone mineral density in healthy premenopausal women does not appear to be significantly affected.[2,3] However, there is limited evidence that adolescents and young women (less than 23 years of age) using oral combined contraceptives have a lower bone mineral density than non-users; it is unclear whether contraceptives might prevent young women from reaching their peak bone mass and put them at increased risk of osteoporosis later in life.[3] There is some evidence of a positive effect on bone mineral density in perimenopausal[2,3] and postmenopausal women[3] taking combined oral contraceptives, but past use in postmenopausal women appeared to have no effect. Although bone mineral density is used as an indicator of fracture risk, the true effects of combined oral contraceptives on this clinical outcome are unclear;[1] there is a particular lack of data in older women, in whom osteoporotic fractures are most common.[3]

There is stronger evidence that bone mineral density is reduced in current users of the depot progestogen-only contraceptive, **medroxyprogesterone acetate.** Recovery occurs after stopping treatment,[4,5] but it is still unclear whether adult women can regain baseline bone mineral density levels, and whether adolescents can reach peak bone mass.[4] There is also a lack of data on fracture risk in both current and former users of all ages.[1,4]

As adolescence is an age at which bone mineral density is normally increasing there is some concern about the possible long-term effects of depot medroxyprogesterone. The UK CSM has advised that in adolescents it should only be used if other methods of contraception are unsuitable or unacceptable, and that there should be a re-evaluation of risks and benefits for women of all ages who wish to continue use beyond 2 years.[6] The FDA has also advised[7] that, for all women, medroxyprogesterone should only be used as a long-term contraceptive, giving an example of more than 2 years, if other contraceptive methods are inadequate. In contrast, however, WHO[8] advises that there should be no restriction, including duration of use, on the use of medroxyprogesterone in women aged 18 to 45 who are otherwise eligible to use it. For adolescents and women over 45, WHO advises that they may use it if the patient and her healthcare provider decide that it is the best method of contraception for her, even if it may decrease her bone density. Others[9] offer similar recommendations in support, pointing out that further research is needed.

There is some evidence that oestrogen supplementation may reduce or prevent the reduction in bone mineral density caused by medroxyprogesterone acetate.[10,11] Although such supplementation could be considered in medroxyprogesterone users who have osteopenia or are at high risk, the optimal dose, route, and extent of benefit has not been established.[9]

1. Lopez LM, *et al.* Steroidal contraceptives: effect on bone fractures in women. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2009 (accessed 25/09/09).
2. Liu SL, Lebrun CM. Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review. *Br J Sports Med* 2006; 40: 11–24.
3. Martins SL, *et al.* Combined hormonal contraception and bone health: a systematic review. *Contraception* 2006; 73: 445–69.
4. Curtis KM, Martins SL. Progestogen-only contraception and bone mineral density: a systematic review. *Contraception* 2006; 73: 470–87.
5. Kaunitz AM, *et al.* Bone mineral density in women aged 25-35 years receiving depot medroxyprogesterone acetate: recovery following discontinuation. *Contraception* 2006; 74: 90–9.
6. MHRA. Updated prescribing advice on the effect of Depo-Provera contraception on bones. Message from Professor G Duff, Chairman of CSM (issued 16th November, 2004). Available at: http://www.mhra.

gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con0194785-RevisionSelectionMethod=Latest (accessed 14/01/08)
7. FDA. Depo-Provera (medroxyprogesterone acetate injectable suspension) (issued November 18, 2004). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm154784.htm (accessed 21/07/10)
8. WHO. Hormonal contraception and bone health (issued 2007). Available at: http://www.who.int/reproductivehealth/topics/family_planning/pbrief_bonehealth.pdf (accessed 21/07/10)
9. Cromer BA, *et al.* Depot medroxyprogesterone acetate and bone mineral density in adolescents—the Black Box Warning: a Position Paper of the Society for Adolescent Medicine. *J Adolesc Health* 2006; 39: 296–301.
10. Cundy T, *et al.* A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. *J Clin Endocrinol Metab* 2003; 88: 78–81.
11. Cromer BA, *et al.* Double-blinded randomized controlled trial of estrogen supplementation in adolescent girls who receive depot medroxyprogesterone acetate for contraception. *Am J Obstet Gynecol* 2005; 192: 42–7.

RHEUMATOID ARTHRITIS. There have been rare reports of arthritis or arthropathies attributed to oral contraceptives, and some large studies have investigated the incidence of rheumatoid arthritis in oral contraceptive users. A negative association between the use of oral contraceptives and the development of rheumatoid arthritis has been reported in some studies thus giving rise to the suggestion that oral contraceptive use may, in fact, have some sort of protective role. These findings were not, however, substantiated by a recent, large, long-term cohort study[1] which found no association, either beneficial or detrimental, between the use of oral contraceptives and the later development of rheumatoid arthritis. An earlier meta-analysis also found no conclusive evidence of a protective effect of oral contraceptives on rheumatoid arthritis risk.[2] There is limited information about the effect of oral contraceptives on pre-existing rheumatoid arthritis. One study[3] found that there was no significant influence on the progression of the disease, but there was a trend towards less radiographic joint damage and disability with long-term oral contraceptive use.

1. Karlson EW, *et al.* Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis Rheum* 2004; 50: 3458–67.
2. Pladevall-Vila M, *et al.* Controversy of oral contraceptives and risk of rheumatoid arthritis: meta-analysis of conflicting studies and review of conflicting meta-analyses with special emphasis on analysis of heterogeneity. *Am J Epidemiol* 1996; 144: 1–14.
3. Drossaers-Bakker KW, *et al.* Pregnancy and oral contraceptive use do not significantly influence outcome in long term rheumatoid arthritis. *Ann Rheum Dis* 2002; 61: 405–8.

Effects on the nervous system. *Headache* is reported as a common adverse effect and frequent reason for stopping combined oral contraceptives. However, a systematic review[1] found that although study results could not be pooled, there was no strong evidence associating combined oral contraceptive use with headache. There may have been an increase in headache in the early cycles, but this tended to improve with continued use; for most women there was no effect on headache activity and some actually reported improvement. Headache also appeared to be associated with oestrogen withdrawal during the tablet-free week of the cycle, but there was no evidence that headache was improved by changing to a preparation with a lower dose of oestrogen. However, some women appeared to be at higher risk, such as those with a strong personal or family history of troublesome headaches, particularly migraine. Combined oral contraceptives are not contra-indicated in women with non-migrainous headache, but they should be used with caution or avoided in women with migraine because of the increased risk of stroke (see Migraine, under Precautions, p. 2241.3).

Chorea has been reported in women using combined oral contraceptives. Reviews of the literature have reported the onset of chorea to range from 1 week to 11 months,[2] with an average of 3 months,[3] and resolution of symptoms after stopping the contraceptive to occur after 1 week to 5 months[2] or an average of 5 weeks.[3] The mechanism of this effect is unclear. Some cases occurred in patients with no history of neurological disease,[2,3] but others had a history of rheumatic fever, often with Sydenham chorea, or chorea gravidarum, chorea secondary to other conditions, or congenital heart disease.[3] There is some evidence that chorea could be mediated by the production of antiphospholipid antibodies, as either a primary antiphospholipid syndrome or secondary to SLE.[4,5] It has been suggested that the production of these antibodies could be aggravated by the oestrogen component of combined oral contraceptives.[4] In another case report[6] it was suggested that the presence of anti-basal ganglia antibodies might have played a role in the development of chorea by making the basal ganglia more susceptible to the effects of the oestrogen component of an oral contraceptive.

It is generally advised that combined oral contraceptives should be used with caution or avoided in women with antiphospholipid antibodies because they are at increased risk of venous thromboembolism, see Cardiovascular Disease, under Precautions, p. 2241.2.

1. Loder EW, *et al.* Headache as a side effect of combination estrogen-progestin oral contraceptives: a systematic review. *Am J Obstet Gynecol* 2005; 193: 636–49.
2. Wadlington WB, *et al.* Chorea associated with the use of oral contraceptives: report of a case and review of the literature. *Clin Pediatr (Phila)* 1981; 20: 804–6.
3. Gallmberti D. Chorea induced by the use of oral contraceptives: report of a case and review of the literature. *Ital J Neurol Sci* 1987; 8: 383–6.
4. Omdal R, Roalso S. Chorea gravidarum and chorea associated with oral contraceptives—diseases due to antiphospholipid antibodies? *Acta Neurol Scand* 1992; 86: 219–20.
5. Cervera R, *et al.* Chorea in the antiphospholipid syndrome: clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine (Baltimore)* 1997; 76: 203–12.
6. Miranda M, *et al.* Oral contraceptive induced chorea: another condition associated with anti-basal ganglia antibodies. *J Neurol Neurosurg Psychiatry* 2004; 75: 327–8.

Effects on the pancreas. There have been reports of pancreatitis secondary to hyperlipidaemia associated with the use of combined oral contraceptives.[1,2]

1. Parker WA. Estrogen-induced pancreatitis. *Clin Pharm* 1983; 2: 75–9.
2. Stuyt PMJ, *et al.* Pancreatitis induced by oestrogen in a patient with type I hyperlipoproteinaemia. *BMJ* 1986; 293: 734.

Effects on the skin. Oral contraceptives may cause chloasma, and those containing androgenic progestogens may cause or aggravate acne and hirsutism. More rarely, oral contraceptives have been implicated in photosensitivity reactions[1] and photosensitivity associated with drug-induced lupus erythematosus.[2] A survey of people using UVA sunbeds at commercial premises in the UK revealed that the prevalence of pruritus, nausea, and skin rashes as adverse reactions to sunbed use was higher in women taking oral contraceptives than in women receiving no medication.[3] There has been a report of hidradenitis suppurativa, a condition resulting in the recurrence of boils at the axillary apocrine sweat glands, anogenital region, and breasts, occurring in 7 women using oral contraceptives.[4] Sweet's syndrome (acute febrile neutrophilic dermatosis) has been described very rarely with hormonal contraceptives. In one case,[5] the reaction started 10 days after beginning a combined oral contraceptive and resolved after stopping the contraceptive and treating with oral and topical corticosteroids. The woman reported that a similar reaction had occurred 6 months earlier with a different combined oral contraceptive. Sweet's syndrome has also occurred 1 month after insertion of a levonorgestrel IUD; the condition was controlled with corticosteroids, but only resolved completely after removal of the IUD.[6]

For mention of the refuted association between oral contraceptives and malignant melanoma, see Skin under Cardinogenicity p. 2236.2. Auto-immune progesterone dermatitis has been reported in women with a history of oral contraceptive use (see p. 2301.3).

1. Cooper SM, George S. Photosensitivity reaction associated with use of the combined oral contraceptive. *Br J Dermatol* 2001; 144: 641–2.
2. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; (Jun.): 508–11.
3. Diffey BL. Use of UV-A sunbeds for cosmetic tanning. *Br J Dermatol* 1986; 115: 67–76.
4. Stellon AJ, Wakelling M. Hidradenitis suppurativa associated with use of oral contraceptives. *BMJ* 1989; 298: 28–9.
5. Sáez M, *et al.* Sweet's syndrome induced by oral contraceptive. *Dermatology* 2002; 204: 84.
6. Hamill M, *et al.* Sweet's syndrome and a Mirena intrauterine system. *J Fam Plann Reprod Health Care* 2004; 30: 115–16.

Effects on the uterus. The Oxford Family Planning Association study found that the risk of developing uterine leiomyomas (uterine fibroids) was reduced by the use of oral contraceptives[1] by about 17% with each 5 years of oral contraceptive use. This was not thought to be due to selective prescribing.[2,3] The authors hypothesised that unopposed oestrogen may be a risk factor for uterine fibroids, and that the reduced risk with oral contraceptives might be analogous to the reduction in endometrial carcinoma seen with these drugs (see p. 2235.2).[1] Other studies[4,5] have also reported a reduced risk of uterine leiomyomas in current users of oral contraceptives, while past users have a risk similar to that in women who have never used oral contraceptives. However, one study[4] did suggest that in women who had first used oral contraceptives at an early age (13 to 16 years) there was a modestly elevated risk. Another case-control study involving 390 women with leiomyomas failed to find a protective (or detrimental) effect with oral contraceptive use.[6] A further cohort study[7] also found no association between oral contraceptive use and leiomyoma formation, but did report a reduced risk with current use of medroxyprogesterone acetate depot injection.

1. Ross RK, *et al.* Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; 293: 359–62. Correction. *ibid.*: 1027.
2. Ratner H. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; 293: 1027.
3. Ross RK, *et al.* Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; 293: 1027.
4. Marshall LM, *et al.* A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. *Fertil Steril* 1998; 70: 432–9.
5. Chiaffarino F, *et al.* Use of oral contraceptives and uterine fibroids: results from a case-control study. *Br J Obstet Gynaecol* 1999; 106: 857–60.
6. Parazzini F, *et al.* Oral contraceptive use and risk of uterine fibroids. *Obstet Gynecol* 1992; 79: 430–3.
7. Wise LA, *et al.* Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. *Am J Epidemiol* 2004; 159: 113–23.

Pelvic inflammatory disease. It has been suggested that oral contraceptives protect against pelvic inflammatory disease. However, although oral contraceptives are thought to reduce the risk of developing acute pelvic inflammatory disease, higher rates of infection of the lower genital tract by *Chlamydia trachomatis*,[1] and, more tentatively, *Neisseria gonorrhoeae*,[2] have been reported. Other studies[3,4] have suggested that oral contraceptive use is associated with reduced symptom severity, but absence of symptoms is not the same as absence of disease: oral contraceptives might reduce the inflammatory reaction to infection, resulting in unrecognised disease and subsequent complications such as tubal infertility and ectopic pregnancy.[5] There is evidence that users of older oral contraceptives containing more than 50 micrograms of oestrogen may have been at increased risk of tubal infertility, particularly if first used before 20 years of age.[6] No increased risk, or an active decrease in risk (depending on age at first use) was reported for formulations containing 50 micrograms or less of oestrogen, which are now favoured.

The possible effects of depot medroxyprogesterone acetate have also been examined and one study[7] suggested that it was associated with an increase in cervical chlamydial and gonococcal infections. However, confounding factors in this study such as sexual practices, a history of infection, and the background pool of infectivity in sexual partners, have been highlighted[8,9] and cast doubt on a true causal relationship between medroxyprogesterone acetate and risk of infection.

1. Washington AE, *et al.* Oral contraceptives, Chlamydia trachomatis infection, and pelvic inflammatory disease: a word of caution about protection. *JAMA* 1985; 253: 2246–50.
2. Louv WC, *et al.* Oral contraceptive use and the risk of chlamydial and gonococcal infections. *Am J Obstet Gynecol* 1989; 160: 396–402.
3. Walner-Hanssen P, *et al.* Decreased risk of symptomatic chlamydial pelvic inflammatory disease associated with oral contraceptive use. *JAMA* 1990; 263: 54–9.
4. Ness RB, *et al.* Hormonal and barrier contraception and risk of upper genital tract disease in the PID Evaluation and Clinical Health (PEACH) study. *Am J Obstet Gynecol* 2001; 185: 121–7.
5. Henry-Suchet J. Hormonal contraception and pelvic inflammatory disease. *Eur J Contracept Reprod Health Care* 1997; 2: 263–7.
6. Cramer DW, *et al.* The relationship of tubal infertility to barrier method and oral contraceptive use. *JAMA* 1987; 257: 2446–50.
7. Morrison CS, *et al.* Hormonal contraceptive use, cervical ectopy, and the acquisition of cervical infections. *Sex Transm Dis* 2004; 31: 561–7.
8. Dayan L, Donovan B. Chlamydia, gonorrhoea, and injectable progesterone. *Lancet* 2004; 364: 1387–8.
9. Warner P. Concerns regarding design, analysis, and interpretation of the Morrison study on hormonal contraceptive use and acquisition of cervical infections. *Sex Transm Dis* 2005; 32: 644.

Precautions

Before hormonal contraceptives are given, the woman should undergo an appropriate medical examination and her medical history should be carefully evaluated. Regular examination is recommended during use. The contraceptive efficacy of combined and progestogen-only preparations may be reduced during episodes of vomiting or diarrhoea and extra contraceptive measures may be necessary during and for 7 days after recovery. For precautions to be taken if doses are missed, see Uses and Administration, p. 2231.3.

Combined hormonal contraceptives are *contra-indicated* in women with markedly impaired liver function or cholestasis, the Dubin-Johnson or Rotor syndromes, hepatic tumour, oestrogen-dependent neoplasms such as breast or endometrial cancer, cardiovascular disease (see also p. 2241.2) including previous or current thromboembolic disorders or high risk of them, and arterial disease or multiple risk factors for it, disorders of lipid metabolism, undiagnosed vaginal bleeding, possible pregnancy, or a history during pregnancy of pruritus or cholestatic jaundice, chorea, herpes gestationis, pemphigoid gestationis, or deteriorating otosclerosis. They are also contra-indicated in severe or focal migraine (or where there are other risk factors for cardiovascular disease) and should be used with caution in other forms of migraine (for further details, see p. 2241.3). Combined hormonal contraceptives should not be used during active trophoblastic disease, or until urine and plasma gonadotrophin concentrations have returned to normal after treatment. They should be *given with caution* to women with a history of clinical depression, gallbladder disease, sickle-cell disease, or conditions influenced by fluid retention. Oral contraceptive absorption, and hence efficacy, may be reduced in women with inflammatory bowel disease when there is small bowel involvement or malabsorption. They should also be used with caution in those with varicose veins, and should be avoided during sclerosing treatment. Where not actually contra-indicated, they should also be used with caution in those with a risk factor for cardiovascular disease such as diabetes mellitus, smoking, obesity, hypertension, or a family history of cardiovascular disorders (see also p. 2241.2). A low-strength combined oral contraceptive (containing 20 micrograms of

ethinylestradiol) may be suitable for women with risk factors for cardiovascular disease, provided a combined oral contraceptive is otherwise suitable. A standard-strength combined hormonal contraceptive (such as a monophasic oral preparation containing 30 or 35 micrograms of ethinylestradiol) may be used in women over the age of 35 years provided they do not smoke and have no other risk factors for cardiovascular disease. Once women are aged over 40 years, the first choice of oral combined hormonal contraceptive should contain the lowest dose of ethinylestradiol that provides adequate cycle control, such that a preparation containing less than 30 micrograms of ethinylestradiol may be suitable. After 50 years of age, women taking a combined hormonal contraceptive should switch to a non-hormonal method or a progestogen-only method (such as a progestogen-only oral contraceptive, progestogen implant, or levonorgestrel intra-uterine device). Use by those undergoing surgery or prolonged bed rest may increase the risk of thromboembolic episodes and it is generally recommended that combined hormonal contraceptives should be stopped 4 weeks before major elective surgery (but see also p. 2242.2). Contact lenses may irritate. The use of combined oral contraceptives may influence the results of certain laboratory tests including liver, thyroid, adrenal, and renal-function tests, plasma concentrations of binding proteins and lipid/lipoprotein fractions, and fibrinolysis and coagulation parameters.

Combined hormonal contraceptives should be *stopped immediately*, and appropriate investigations and treatment carried out, if any of the following occur:

- sudden severe chest pain, sudden breathlessness, or severe pain/swelling in calf of one leg (possibly indicative of thromboembolic complications)
- unusual, severe, prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body, or other signs or symptoms suggestive of cerebrovascular accident
- a first unexplained epileptic seizure
- hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain
- significant rise in blood pressure (above 160 mmHg systolic or 95 mmHg diastolic)
- clear exacerbation of other conditions known to be capable of deteriorating during oral contraception or pregnancy.

Progestogen-only contraceptives, whether oral or injectable, may be used when oestrogen-containing preparations are contra-indicated but certain contra-indications and precautions must still be observed. They are contra-indicated in women with undiagnosed vaginal bleeding, possible pregnancy, severe arterial disease, hormone-dependent neoplasms, and severe liver disease such as hepatic tumour.

Like combined hormonal contraceptives they should not be used during active trophoblastic disease. Progestogen-only contraceptives should be used with caution in women with arterial disease, malabsorption syndromes, liver dysfunction including recurrent cholestatic jaundice, or a history of jaundice in pregnancy. Oral progestogen-only contraceptives should also be used with caution in past ectopic pregnancy (see p. 2236.3) or functional ovarian cysts. Despite unsatisfactory evidence of hazard, other suggested cautions for progestogen-only contraceptives include diabetes mellitus, hypertension, migraine, and thromboembolic disorders.

Breast feeding. Progestogen-only contraceptives are the hormonal contraceptives of choice for breast-feeding women because they do not affect lactation,[1] but recommendations vary about when they can or should be started, and may not match licensed product information. Some guidelines[2] recommend that all progestogen-only methods can be started 6 weeks after birth. Others[3] suggest that oral preparations can be started any time in breast-feeding women, although they are not needed before 3 weeks postpartum. Progestogen-only parenteral contraceptives, such as medroxyprogesterone acetate, are usually not given until 6 weeks postpartum;[1-3] troublesome bleeding can occur before this time.[3] The etonogestrel subdermal implant may be inserted at 3 weeks postpartum. The levonorgestrel IUD may also be used during lactation, although insertion should be delayed because of an increased risk of perforation of the uterine wall or cervix. Licensed product information advises waiting until 6 weeks after delivery, but others[3] suggest that it may be inserted from 4 weeks postpartum (with additional contraceptive cover for the first 7 days if necessary).

Combined hormonal contraceptives may reduce the volume of breast milk and are therefore avoided in breast-feeding women for the first 6 weeks after birth.[1,3] In general, they are not recommended for 6 months or until weaning.[2,3] Between 6 weeks and 6 months postpartum, some[3] suggest that they may be considered for women who are fully breast feeding if other contraceptive methods are unacceptable. It is also consider that for women who are partially or token breast feeding during this time, the benefits of combined hormonal contraception may outweigh the risks.

Very small amounts of oestrogens and progestogens from hormonal contraceptives are distributed into breast milk, but there is no indication that this adversely affects development of the breast-fed infant.[3,4] The American Academy of Pediatrics[5] has also reviewed the use of hormonal contraceptives during lactation, commenting that early information was based on the use of high-dose contraceptives. It was noted that there might be a decrease in milk production, but that there was insufficient information to confirm that there was any alteration in the composition of breast milk, and that although there had been rare cases of gynaecomastia in breast-fed infants of mothers who received high-dose contraceptives, there was no consistent evidence of long-term adverse effects on the infant. A later study[6] of 48 children whose mothers had received high-dose combined oral contraceptives during breast feeding found no effect on these children compared with controls, up to 8 years of age. The Academy therefore considers[7] that combined oral contraceptives are usually compatible with breast feeding.

Breast feeding itself suppresses ovulation and can be used, if started immediately postpartum, as the lactational amenorrhoea method of contraception; for further details, see Contraception, p. 2232.3.

1. Queenan JT. Contraception and breastfeeding. *Clin Obstet Gynecol* 2004; 47: 734–9.
2. Hatcher RA, *et al. The essentials of contraceptive technology: a handbook for clinical staff.* Baltimore: John Hopkins Bloomberg School of Public Health, Population Information Program, 2003. Also available at: http://www.infoforhealth.org/pubs/ect/ (accessed 14/01/08)
3. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Clinical guidance: postnatal sexual and reproductive health (issued September 2009). Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidancePostnatal09.pdf (accessed 09/10/09)
4. Fraser IS. A review of the use of progestogen-only minipills for contraception during lactation. *Reprod Fertil Dev* 1991; 3: 245–54.
5. American Academy of Pediatrics Committee on Drugs. Breast-feeding and contraception. *Pediatrics* 1981; 68: 138–40. Also available at: http://pediatrics.aappublications.org/cgi/reprint/68/1/138.pdf (accessed 14/01/08)
6. Nilsson S, *et al.* Long-term follow-up of children breast-fed by mothers using oral contraceptives. *Contraception* 1986; 34: 443–57.
7. 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 14/01/08)

Cardiovascular disease. Combined hormonal contraceptives are associated with several arterial and venous risks. Progestogen-only contraceptives are associated with fewer risks, although they still need to be avoided when arterial disease is severe.

Arterial disease. In the UK the *BNF* has recommended that combined hormonal contraceptives may be used with **caution** if any **one** of the following factors are present, but should be **avoided** if **two or more** factors are present:

- *family history of arterial disease* in first-degree relative aged under 45 years (avoid if there is also an atherogenic lipid profile)
- *diabetes mellitus* (avoid if diabetic complications are present)
- *hypertension* (avoid if blood pressure is above systolic 160 mmHg or diastolic 95 mmHg)
- *smoking* (avoid if 40 or more cigarettes are smoked daily)
- *age over 35 years* (avoid if over 50 years)
- *obesity* (avoid if BMI $\geq 35\ kg/m^2$, unless no suitable alternative)
- *migraine*, see under Migraine, below

Venous thromboembolism. Combined hormonal contraceptives increase the risk of venous thromboembolism and should not be used in women with a personal history of venous or arterial thrombosis. In addition they should be used with **caution** if any **one** of the following risk factors are present, but should be **avoided** if **two or more** factors are present:

- *family history of venous thromboembolism* in first-degree relative aged under 45 years (avoid if there is a known prothrombotic coagulation abnormality such as antiphospholipid antibodies, which may occur in patients with SLE, or factor V Leiden)
- *long-term immobilisation* such as wheelchair use (avoid if confined to bed or with a leg in plaster)
- *history of superficial thrombophlebitis*
- *smoking*
- *age over 35 years* (avoid if over 50 years)
- *obesity*—BMI $\geq 30\ kg/m^2$ (avoid if BMI $\geq 35\ kg/m^2$, unless no suitable alternative)

The *BNF* also advises that women taking combined hormonal contraceptives may be at an increased risk of deep-vein thrombosis during *travel* involving prolonged periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey, and possibly by wearing graduated compression hosiery.

In the light of evidence indicating an increased risk of venous thromboembolism with combined oral contraceptives containing *desogestrel* or *gestodene* (see Venous Thromboembolism, under Effects on the Cardiovascular System, p. 2238.1), the UK CSM advised additional precautions for these products. As well as the usual precautions, it was initially advised they should not be used by obese women (BMI greater than $30\ kg/m^2$), those with varicose veins, or those with a history of thrombosis of any cause. Moreover, it was also recommended that they should be used only by women who were intolerant of other combined oral contraceptives and who were prepared to accept an increased risk of venous thromboembolism. Subsequently the CSM[1] modified its advice as follows: they recommended that these products should be avoided in women with known risk factors for venous thromboembolism. However, in women without contra-indications, the type of combined contraceptive was considered a matter of clinical judgement and personal choice, as long as the woman was fully informed of the small excess risk associated with desogestrel- and gestodene-containing products.

1. CSM/MCA. Combined oral contraceptives containing desogestrel or gestodene and the risk of venous thromboembolism. *Current Problems* 1999; 25: 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023234&RevisionSelectionMethod=LatestReleased (accessed 14/01/08)

Lupus erythematosus. SLE is an auto-immune disease that is far more common in women than in men, and usually has a peak onset for women in their 20s and 30s. There is some evidence to suggest that oral contraceptive use may be associated with a slightly increased risk in the onset of SLE.[1-3] There are also reports and studies of the effect of contraceptives on disease exacerbation, although there has been an apparent reduction in reports which has coincided with the lowering of oestrogen content in contraceptive preparations.[2] More recently, controlled studies[4,5] have found that disease activity and flares over 12 months in women with stable SLE were similar whether they were given a combined oral contraceptive (containing ethinylestradiol 30 or 35 micrograms), a progestogen-only oral preparation, placebo, or copper IUD. However, patients with major disease, such as lupus nephritis, could be at greater risk of exacerbation. It is also generally advised that combined oral contraceptives should be avoided in women with antiphospholipid antibodies (which includes about a third of all patients with SLE) because they are at increased risk of venous thromboembolism.[1,2]

1. Petri M. Exogenous estrogen in systemic lupus erythematosus: oral contraceptives and hormone replacement therapy. *Lupus* 2001; 10: 222–6.
2. Mok CC, *et al.* Use of exogenous estrogens in systemic lupus erythematosus. *Semin Arthritis Rheum* 2001; 30: 426–35.
3. Costenbader KH, *et al.* Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007; 56: 1251–62.
4. Sánchez-Guerrero J, *et al.* A trial of contraceptive methods in women with systemic lupus erythematosus. *N Engl J Med* 2005; 353: 2539–49.
5. Petri M, *et al.* Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005; 353: 2550–8.

Migraine. Both migraine and the use of combined oral contraceptives have been identified as risk factors for ischaemic stroke. A systematic review[1] concluded that in women with a history of migraine, users of combined oral contraceptives were 2 to 4 times more likely to have an ischaemic stroke than non-users. It was unclear, however, whether this increase in relative risk was due to independent effects of contraceptives and migraine, or whether contraceptive use had a greater effect in women with a history of migraine than in those without.

In the UK the *BNF* has recommended that combined hormonal contraceptives be **contra-indicated** in:

- migraine with typical focal aura
- severe migraine frequently lasting longer than 72 hours despite treatment
- migraine treated with an ergot derivative

It also recommends **caution** in migraine without focal aura. A woman receiving a combined hormonal contraceptive should report any increase in headache frequency or the onset of focal symptoms. If focal neurological symptoms not typical of aura persist for longer than 1 hour the contraceptive should be discontinued and the woman referred urgently to a neurologist.

Other risk factors for arterial disease should also be considered in women with a history of migraine (see Cardiovascular Disease, above).

1. Curtis KM, *et al.* Use of combined oral contraceptives among women with migraine and nonmigrainous headaches: a systematic review. *Contraception* 2006; 73: 189–94.

Obesity. It has been suggested that higher body-weight or BMI might be associated with a greater risk of oral contraceptive failure. Several cohort and case-control studies have evaluated this association, with mixed results that may have been confounded by recall bias, inaccuracy

of reported body-weight, noncompliance, and change in oestrogen dose over time. Some studies have suggested that there is an increased risk of contraceptive failure,[1,2] while others have found no association.[3] In addition, some have found a weak association that was no longer statistically significant when results were adjusted for confounders such as education, income, and ethnicity.[4,5] It is therefore unclear whether an association exists, but obesity is a risk factor for cardiovascular disease and combined oral contraceptives should be used with caution, or avoided, in these women (see Cardiovascular Disease, p. 2241.2).

1. Holt VL, *et al.* Body weight and risk of oral contraceptive failure. *Obstet Gynecol* 2002; **99:** 820–7.
2. Holt VL, *et al.* Body mass index, weight, and oral contraceptive failure risk. *Obstet Gynecol* 2005; **105:** 46–52.
3. Vessey M, Painter R. Oral contraceptive failures and body weight: findings in a large cohort study. *J Fam Plann Reprod Health Care* 2001; **27:** 90–1.
4. Brunner LR, Hogue CJ. The role of body weight in oral contraceptive failure: results from the 1995 national survey of family growth. *Ann Epidemiol* 2005; **15:** 492–9.
5. Brunner Huber LR, *et al.* Body mass index and risk for oral contraceptive failure: a case-cohort study in South Carolina. *Ann Epidemiol* 2006; **16:** 537–43.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies many progestogen-only and combined hormonal contraceptives as porphyrinogenic or as probably porphyrinogenic; they should be prescribed only for compelling reasons and precautions should be taken or considered in all patients.[1]

The *BNF* suggests that progestogens are more hazardous than oestrogens, and that they should be avoided whenever possible. However, progestogens may be used with extreme caution if non-hormonal contraception is inappropriate and potential benefit outweighs the risk. The risk of an acute attack is greatest in women who have had a previous attack or are under 30 years of age. Long-acting progestogen preparations should never be used in those at risk.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. In contrast to the numerous cases of congenital malformations reported after the use of high doses of sex hormones formerly used for hormonal pregnancy tests, there have been only a few suggestions that continued use of oral contraceptives during early pregnancy may result in congenital limb reduction deformities,[1-3] and one case of neonatal choreoathetosis after prenatal exposure to oral contraceptives.[4]

Many studies, conversely, have shown no evidence that the use of oral contraceptives is associated with congenital malformations or teratogenic effects, whether past use (stopped before conception), use after the last menstrual period, or known use in early pregnancy. A meta-analysis[5] confirmed this; the relative risk for all malformations with use of oral contraceptives was estimated to be 0.99 (95% confidence intervals 0.83 to 1.19). The use of oral contraceptives in early pregnancy also appears unlikely to increase the risk of hypospadia in male fetuses[6,7] (see also under Precautions of Estradiol, p. 2273.3).

Depot intramuscular medroxyprogesterone acetate is a highly effective contraceptive, but failures do occur rarely. A review[8] of such failures had limited data on birth outcome in 100 women who continued the pregnancy, but no abnormalities or fetal anomalies were reported.

In 25 pregnancies that were continued after the failure of levonorgestrel-based emergency contraception,[9] there was 1 case of gastro-oesophageal reflux requiring medical treatment and 1 case of nasolachrymal duct obstruction that was surgically drained, but compared with a control group and expected baseline risk there was no increased risk of congenital or genital abnormalities.

For a discussion of the ectopic pregnancy risk in users of hormonal contraceptives, see p. 2236.3.

1. Janerich DT, *et al.* Oral contraceptives and congenital limb reduction defects. *N Engl J Med* 1974; **291:** 697–700.
2. McCredie J, *et al.* Congenital limb defects and the pill. *Lancet* 1983; **ii:** 623.
3. Kricker A, *et al.* Congenital limb reduction deformities and use of oral contraceptives. *Am J Obstet Gynecol* 1986; **155:** 1072–8.
4. Profumo R, *et al.* Neonatal choreoathetosis following prenatal exposure to oral contraceptives. *Pediatrics* 1990; **86:** 648–9.
5. Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstet Gynecol* 1990; **76:** 552–7.
6. Raman-Wilms L, *et al.* Fetal genital effects of first trimester sex hormone exposure: a meta-analysis. *Obstet Gynecol* 1995; **85:** 141–9.
7. Wogelius P, *et al.* Maternal use of oral contraceptives and risk of hypospadias—a population-based case-control study. *Eur J Epidemiol* 2006; **21:** 777–81.
8. Borgatta L, *et al.* Pregnancies diagnosed during Depo-Provera use. *Contraception* 2002; **66:** 169–72.
9. De Santis M, *et al.* Failure of the emergency contraceptive levonorgestrel and the risk of adverse effects in pregnancy and on fetal development: an observational cohort study. *Fertil Steril* 2005; **84:** 296–9.

Sickle-cell disease. *Sickle-cell disease* and oral contraceptive use are both associated with an increased risk of thrombosis but it is by no means certain that the two risks are additive. Study of a small number of women with sickle-cell disease found that combined and progestogen-only contraceptives had no effect on red cell deformability.[1] Licensed product information for some preparations has specifically warned against the use of combined oral contraceptives in sickle-cell disease. However, there is a lack of strong clinical evidence to support such a contra-indication,[2,3] and there is some suggestion that progestogen-only contraception may be associated with improvements in clinical symptoms and sickle-cell crises.[4] WHO considers[5] that in women with sickle-cell disease the benefits generally outweigh the risks for low-dose combined oral contraceptives (35 micrograms or less of ethinylestradiol) and other forms of combined hormonal contraceptives (injectable, transdermal patch, and vaginal ring), and that there is no restriction for the use of progestogen-only contraceptives (oral, depot injection, implant, and intra-uterine device).

For *sickle-cell trait* there is no increased risk of thrombosis and no contra-indication to the use of a combined or progestogen-only preparation. Many women with sickle-cell trait have, unnecessarily, been denied the use of oral contraceptives in the mistaken belief that advice for sickle-cell disease applies to the trait.[6]

1. Yoong WC, *et al.* Red cell deformability in oral contracepuve pill users with sickle cell anaemia. *Br J Haematol* 1999; **104:** 868–70.
2. Freie HMP. Sickle cell diseases and hormonal contraception. *Acta Obstet Gynecol Scand* 1983; **62:** 211–17.
3. Howard RJ, *et al.* Contraceptives, counselling, and pregnancy in women with sickle cell disease. *BMJ* 1993; **306:** 1735–7.
4. Legardy JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review. *Contraception* 2006; **73:** 195–204.
5. WHO. *Medical eligibility criteria for contraceptive use.* Fourth ed. Geneva: WHO, 2009. Available at: http://whqlibdoc.who.int/publications/2009/9789241563888_eng.pdf (accessed 21/07/10)
6. Evans DIK. Should patients who say that they have "sickle cells" be prescribed the contraceptive pill? *BMJ* 1984; **289:** 425.

Surgery. Case reports and epidemiological studies showing an increased risk of idiopathic deep-vein thrombosis and pulmonary embolism in young women taking **combined oral contraceptives** (see Venous Thromboembolism, p. 2238.1) led to the widespread belief that oral contraceptives may predispose to deep-vein thrombosis postoperatively. In consequence, the advice commonly given in the UK has been that, if possible, combined oral contraceptives should be stopped 4 weeks before major elective surgery and all surgery of the legs, and that prophylactic heparin should be considered where this was not possible.[1] They can normally be started again at the first menses occurring at least 2 weeks after full mobilisation. However, estimates of the size of the risk are variable;[2-5] one report[2] found that the incidence of deep-vein thrombosis postoperatively in young women taking combined oral contraceptives was about twice that of women not taking contraceptives but the difference was not statistically significant. Some have considered[6] that the risk to young women of becoming pregnant after stopping oral contraceptives, or of developing adverse effects from heparin prophylaxis, may be greater than the risk of developing postoperative deep-vein thrombosis. This is in line with the views of the Thromboembolic Risk Factors (THRIFT) Consensus Group.[7] They suggested that unless there were other risk factors there was insufficient evidence to support a policy of routinely stopping combined oral contraceptives before major surgery. Additionally, there was insufficient evidence to support routine specific thromboembolic prophylaxis in women without additional risk factors. A review[8] has subsequently recommended that women for whom major elective surgery was planned should continue taking the combined oral contraceptive but should receive thromboprophylaxis in the perioperative period. It has also been pointed out[9,10] that for patients awaiting surgery who require contraception, a progestogen-only oral contraceptive or an injection of medroxyprogesterone acetate may be suitable since neither preparation increases the risk of thrombosis.

1. Guillebaud J. Surgery and the pill. *BMJ* 1985; **291:** 498–9.
2. Vessey M, *et al.* Oral contraceptives and venous thromboembolism: findings in a large prospective study. *BMJ* 1986; **292:** 526.
3. Tso SC, *et al.* Deep vein thrombosis and changes in coagulation and fibrinolysis after gynaecological operations in Chinese: the effect of oral contraceptives and malignant disease. *Br J Haematol* 1980; **46:** 603–12.
4. Gallus AS, *et al.* Oral contraceptives and surgery: reduced antithrombin and antifactor XA levels without postoperative venous thrombosis in low-risk patients. *Thromb Res* 1984; **35:** 513–26.
5. Sagar S, *et al.* Oral contraceptives, antithrombin III activity, and postoperative deep-vein thrombosis. *Lancet* 1976; **i:** 509–11.
6. Sue-Ling H, Hughes LE. Should the pill be stopped preoperatively? *BMJ* 1988; **296:** 447–8.
7. Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992; **305:** 567–74.
8. Anonymous. Drugs in the peri-operative period: hormonal contraceptives and hormone replacement therapy. *Drug Ther Bull* 1999; **37:** 78–80.
9. Guillebaud J. Should the pill be stopped preoperatively? *BMJ* 1988; **296:** 786–7.
10. Guillebaud J, Robinson GE. Stopping the pill. *BMJ* 1991; **302:** 789.

Travel. For a warning that women taking oral contraceptives may be at increased risk of deep-vein thrombosis from travel involving prolonged immobility see Cardiovascular Disease, p. 2241.2.

Interactions

Enzyme-inducing drugs have the potential to cause combined hormonal contraceptives to fail by increasing their metabolism and clearance. This effect is well established for several *antiepileptics* and *rifamycin antibacterials*, and is likely for some *antivirals*. Although less well documented, these interactions would also be expected to apply to most progestogen-only contraceptives.

The *Faculty of Sexual and Reproductive Healthcare (FSRH)* in the UK has provided recommendations for contraception in women taking enzyme-inducing drugs.

- All women should be advised to use a reliable contraceptive method that is unaffected by enzyme-inducing drugs; these include the progestogen-only injectables (medroxyprogesterone and norethisterone enantate), the levonorgestrel-releasing IUD, copper IUDs, and barrier methods. They should be used to cover the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping it.
- For women taking a combined hormonal contraceptive (oral, transdermal patch, or vaginal ring) who require a short course (no more than 2 months) of an enzyme-inducing drug and do not want to change to a different method of contraception, the hormonal contraceptive may be continued with additional non-hormonal contraceptive methods (e.g. condoms). The hormonal contraceptive should be used in a tricycling or extended regimen: a tricycling regimen consists of taking three 21-day cycles continuously without a break followed by a shortened break of 4 days; in an extended regimen the hormonal contraceptive is taken continuously (for not less than 3 weeks) until breakthrough bleeding occurs, at which time a shortened break of 3 to 4 days may be taken. If the contraceptive is being given orally it must be a monophasic preparation and should provide at least 30 micrograms of ethinylestradiol daily. The efficacy of these regimens is uncertain however.
- For women taking a combined hormonal contraceptive who require long-term treatment (more than 2 months) with an enzyme-inducing drug and do not want to change to a different method of contraception, or when there are difficulties in using additional contraceptive precautions during short courses, an alternative is to use a combined oral contraceptive in a regimen that provides ethinylestradiol 50 micrograms or more daily (maximum 70 micrograms daily) in a tricycling or extended regimen. The use of two patches or two vaginal rings simultaneously is not recommended. However, these measures are **not** sufficient for long-term use of rifamycins, and an alternative method such as an IUD is always recommended.
- For women taking a progestogen-only oral contraceptive or using an implant, an additional non-hormonal or alternative method of contraception is recommended to cover short courses of enzyme-inducing drugs. An alternative method of contraception should be used if long-term treatment with an enzyme-inducing drug is required.
- For women requiring postcoital (emergency) contraception during or in the 4 weeks after stopping enzyme-inducing drugs, a single oral dose of levonorgestrel 3 mg given within 120 hours of intercourse has been suggested. Alternatively, a copper IUD may be used.

Combined oral contraceptive failure has been attributed to an interaction with *broad-spectrum antibacterials*, purportedly through a reduction in the enterohepatic recycling of the oestrogen component. However, the evidence does not generally support such an interaction and the FSRH advises that additional contraceptive precautions are not necessary during or after courses of antibacterials that do not induce liver enzymes. Nevertheless, if the antibacterial causes vomiting or diarrhoea then the advice for missed doses should be considered (see Uses, p. 2231.3).

Further details of drugs affecting hormonal contraceptives are given below under specific headings.

Oral contraceptives may also *affect other drugs*. Compounds undergoing oxidative metabolism can have their plasma concentration raised by oral contraceptives through an inhibitory action. Conversely, oral contraceptives appear to induce glucuronidation of some drugs thus reducing their plasma concentration. Oral contraceptives can also antagonise the actions of several drugs. Drugs affected include:

- some analgesics (increased clearance of paracetamol and morphine)
- anticoagulants (increased and decreased effects reported; see p. 1535.1)
- some antidepressants (reduced efficacy, but also increased toxicity; see p. 407.2)

- antidiabetics (antagonism of effect)
- the antiepileptic lamotrigine (decreased plasma concentrations; see p. 530.2)
- antihypertensives (antagonism of effect)
- benzodiazepines (increased or decreased clearance; see p. 1070.2)
- ciclosporin (increased toxicity; see p. 1955.1)
- clofibrate (increased clearance and antagonism of effect)
- corticosteroids (enhanced effect; see p. 1620.3)
- levothyroxine (reduced free fraction due to increased binding globulin concentration; see p. 2342.2)
- lidocaine (increased free fraction due to altered protein binding; see Protein Binding, under Pharmacokinetics, p. 1991.3)
- melatonin (increased concentrations; see p. 2552.2)
- selegiline (decreased clearance; see p. 916.2)
- tizanidine (reduced clearance; see p. 2027.2)
- xanthines (decreased clearance; see p. 1236.2)

Reviews.

1. Back DJ, Orme ML'E. Pharmacokinetic drug interactions with oral contraceptives. *Clin Pharmacokinet* 1990; 18: 472–84.
2. Shenfield GM. Oral contraceptives: are drug interactions of clinical significance? *Drug Safety* 1993; 9: 21–37.
3. Quereux C, Bory JP. Interaction médicamenteuse et contraception orale. *Contracept Fertil Sex* 1998; 26: 129–31.
4. Schwartz JB. Oral contraceptive therapy in women: drug interactions and unwanted outcomes. *J Gend Specif Med* 1999; 2: 26–9.
5. Ellisman A. Interactions with hormonal contraception. *Br J Fam Plann* 2000; 26: 109–11. Correction. *Ibid.*: 151.
6. Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit. Drug interactions with hormonal contraception (issued January 2011). Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceDrugInteractionsHormonal.pdf (accessed 18/04/11)

Antibacterials. An interaction between the *rifamycins (rifampicin* and *rifabutin)* and hormonal contraceptives is well established and alternative contraceptive measures are necessary (see Rifamycins, below).

A variety of *broad-spectrum antibacterials* have also been reported to decrease oral contraceptive efficacy. Some studies have pointed to interference with intestinal flora involved in enterohepatic circulation of oestrogens as being a likely mechanism for this interaction. Although up until 1985 there had been 32 reports[1] of unintended pregnancies in women receiving *penicillins* (25 of them with *ampicillin*) the ability of antibacterials to inhibit oral contraceptive efficacy remains unproven. The data are consistent, however, with the supposition that efficacy is occasionally impaired.[2] Several cases of unintended pregnancies have been reported after the use of *tetracyclines*. With regard to other antibacterials, in theory any one with significant effects on intestinal flora could affect contraceptive efficacy. Isolated cases of pregnancy have been reported following the use of *cephalosporins, chloramphenicol, dapsone, isoniazid, nitrofurantoin, sulfonamides,* and *co-trimoxazole* but it is impossible to determine which, if any, of these interactions is real.

Advice on the use of broad-spectrum antibacterials with combined hormonal contraceptives has traditionally been cautious, despite the lack of strong evidence of an interaction. It was usually recommended that additional contraceptive precautions should be used while taking, and for 7 days after stopping, a short course of any broad-spectrum antibacterial. It was also suggested that if the course of antibacterial exceeded 3 weeks the intestinal flora would develop resistance making additional precautions unnecessary, unless a new antibacterial was started. However, a review[3] of the evidence by the Faculty of Sexual Health and Reproduction (UK) concluded that overall the evidence did not generally support an interaction, and advised that additional contraceptive precautions are not necessary during or after courses of antibacterials that do not induce liver enzymes. This advice was in agreement with contemporaneous advice issued by WHO and CDC. Nevertheless, if the antibacterial causes vomiting or diarrhoea then the advice for missed doses should be considered (see Uses, p. 2231.3).

1. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; 25: 527–32.
2. Dickinson BD, *et al.* Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2001; 98: 853–60.
3. Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit. Drug interactions with hormonal contraception (issued January 2011). Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceDrugInteractionsHormonal.pdf (accessed 18/04/11)

RIFAMYCINS. Rifampicin regularly results in menstrual irregularities and occasionally in unintended pregnancies in women receiving oral contraceptives. It is a potent enzyme inducer and considerably enhances the metabolism of hormonal contraceptives. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, including rifamycins, see Interactions, p. 2242.3.

Similar precautions are recommended during *rifabutin* therapy.

Contraceptive failure, resulting in an ectopic pregnancy, has also been reported in a woman who started rifampicin therapy 3 months after placement of an etonogestrel implant.[1]

1. Patni S, *et al.* Ectopic pregnancy with Implanon. *J Fam Plann Reprod Health Care* 2006; 32: 115.

TROLEANDOMYCIN. Severe pruritus and jaundice may occur if oral contraceptives and troleandomycin are given together.[1] It has been suggested that their hepatic effects may be additive or synergistic, and that concurrent use should be avoided.

1. Miguet J-P, *et al.* Jaundice from troleandomycin and oral contraceptives. *Ann Intern Med* 1980; 92: 434.

Antidepressants. *St John's wort* may decrease blood concentrations of oral contraceptives by enzyme induction.[1-3] There have been reports of intermenstrual bleeding and altered menstrual bleeding in women on long-term oral contraceptives who started taking St John's wort.[4] Several pregnancies have also been reported.[5,6]

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3.

1. Hall SD, *et al.* The interaction between St John's wort and an oral contraceptive. *Clin Pharmacol Ther* 2003; 74: 525–35.
2. Pfrunder A, *et al.* Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. *Br J Clin Pharmacol* 2003; 56: 683–90.
3. Murphy PA, *et al.* Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception* 2005; 71: 402–8.
4. Yue Q-Y, *et al.* Safety of St. John's wort (Hypericum perforatum). *Lancet* 2000; 355: 576–7.
5. Läkemedelsverket (Medical Products Agency—Sweden). Minskad effekt av p-piller vid samtidig användning av johannesört har lett till oönskad graviditet (issued 4th February, 2002). Available at: http://www.lakemedelsverket.se/Tpl/NewsPage%5F%5F%5F%5F580.aspx (accessed 20/08/10)
6. Schwarz UI, *et al.* Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception. *Br J Clin Pharmacol* 2003; 55: 112–13.

Antiepileptics. Oral contraceptive failure and breakthrough bleeding have been reported in numerous cases during antiepileptic therapy.[1,2] *Phenytoin,* barbiturates such as *phenobarbital* and *primidone,* and *carbamazepine* have been most frequently implicated, and *oxcarbazepine, felbamate,* and *topiramate* may interact similarly.[3] These drugs increase the clearance of both oestrogens and progestogens by enzyme induction, so diminishing their effects. Contraceptive methods that are not affected by enzyme induction include a copper or levonorgestrel IUD, or intramuscular depot medroxyprogesterone acetate.[4,5] If these are unsuitable, a combined oral contraceptive with an increased oestrogen content equivalent to ethinylestradiol 50 micrograms or more, and a corresponding increase in progestogen, is generally recommended. In addition, the use of a monophasic preparation given for 3 cycles without a break followed by a tablet-free interval of 4 days (tricycling) has also been suggested.[4] The importance of the progestogen in suppressing ovulation has also been discussed, with the suggestion that ethinylestradiol doses of less than 50 micrograms could be used provided the dose of progestogen is at least 1 mg of norethisterone, 150 micrograms of levonorgestrel, or 300 micrograms of norgestrel.[5] Biphasic, triphasic, and progestogen-only oral contraceptives are not recommended.[5]

Lamotrigine may also reduce contraceptive efficacy, and is markedly affected in turn by the contraceptive (see p. 530.2). Contraceptive efficacy may also be reduced, in a dose-dependent manner, by *perampanel* (see p. 535.2).

For the effects of oral contraceptives on *valproate,* see p. 558.1.

The efficacy of postcoital hormonal contraception (emergency contraception) is also reduced by enzyme-inducing antiepileptic drugs,[4] and an increased dose has been suggested (see Interactions, p. 2242.3).

Antiepileptics that are reported not to affect hormonal contraceptives include *ethosuximide, gabapentin, levetiracetam, tiagabine, valproate,* and *vigabatrin.*[4,5]

1. Mattson RH, Cramer JA. Epilepsy, sex hormones, and antiepileptic drugs. *Epilepsia* 1985; 26 (suppl 1): S40–S51.
2. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; 25: 527–32.
3. Wilbur K, Ensom MHH. Pharmacokinetic drug interactions between oral contraceptives and second-generation anticonvulsants. *Clin Pharmacokinet* 2000; 38: 355–65.
4. O'Brien MD, Guillebaud J. Contraception for women with epilepsy. *Epilepsia* 2006; 47: 1419–22.
5. Thorneycroft I, *et al.* The impact of antiepileptic drug therapy on steroidal contraceptive efficacy. *Epilepsy Behav* 2006; 9: 31–9.

Antifungals. Menstrual irregularities and pregnancies have been reported in women receiving oral contraceptives and *griseofulvin.*[1,2] It has been described as an inducer of hepatic enzymes that may increase the metabolism of hormonal contraceptives, but clinical evidence for this mechanism of interaction is lacking. Nevertheless, additional contraceptive measures should be considered during concomitant use and after stopping griseofulvin; for general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3. There have also been anecdotal reports[3-5] of menstrual irregularities and contraceptive failure with *fluconazole, itraconazole,* and *ketoconazole,* and similar advice applies to these if pregnancy is to be avoided with certainty.

1. van Dijke CPH, Weber JCP. Interaction between oral contraceptives and griseofulvin. *BMJ* 1984; 288: 1125–6.
2. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; 25: 527–32.
3. Pillans PI, Sparrow MJ. Pregnancy associated with a combined oral contraceptive and itraconazole. *N Z Med J* 1993; 106: 436.
4. Meyboom RHB, *et al.* Disturbance of withdrawal bleeding during concomitant use of itraconazole and oral contraceptives. *N Z Med J* 1997; 110: 300.
5. van Puijenbroek EP, *et al.* Verstoring van de plicyclus tijdens het gelijktijdig gebruik van itraconazol en orale anticonceptiva. *Ned Tijdschr Geneeskd* 1998; 142: 146–9.

Antivirals. Some antivirals are likely to accelerate the metabolism of oestrogens and progestogens; theoretically therefore, they may decrease the efficacy of hormonal contraceptives. This has been suggested for HIV-protease inhibitors such as *nelfinavir,*[1] *ritonavir,*[2] and ritonavir-boosted HIV-protease inhibitors, and for the NNRTI *nevirapine.*[3] An alternative form of contraception should be considered. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3.

Conversely, the area under the plasma-concentration-time curve for ethinylestradiol is reported to be increased by HIV-protease inhibitors such as *amprenavir, atazanavir,* and *indinavir,* and the NNRTIs *delavirdine* and *efavirenz.* Although the clinical implications are unknown, the licensed product information recommends alternative or additional contraception.

The use of condoms with a long-acting method, such as an injectable contraceptive, may be more suitable for patients with HIV infection or at risk of infection.

1. Clark RA, Theall K. Population-based study evaluating association between selected antiretroviral therapies and potential oral contraceptive failure. *J Acquir Immune Defic Syndr* 2004; 37: 1219–20.
2. Ouellet D, *et al.* Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol* 1998; 46: 111–16.
3. Mildvan D, *et al.* Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. *J Acquir Immune Defic Syndr* 2002; 29: 471–7.

Endothelin receptor antagonists. In a pharmacokinetic study of healthy women[1] the area under the concentration-time curve (AUC) of both ethinylestradiol and norethisterone were reduced by *bosentan,* probably by enzyme induction. The possibility of contraceptive failure should be considered, and licensed product information for bosentan suggests that an additional or alternative method of contraception should be used during bosentan therapy. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3.

In contrast, *sitaxentan* is an inhibitor of some cytochrome P450 isoenzymes, and it has increased exposure to ethinylestradiol and norethisterone in women taking a combined oral contraceptive. An increase in oestrogen exposure may possibly increase the risk of thromboembolism.

1. van Giersbergen PLM, *et al.* Pharmacokinetic interaction between bosentan and the oral contraceptives norethisterone and ethinyl estradiol. *Int J Clin Pharmacol Ther* 2006; 44: 113–18.

Mifepristone. The antiprogestogen effect of mifepristone will interfere with the effectiveness of hormonal contraceptives. A non-hormonal method of contraception should be used by women given continuous mifepristone for conditions such as Cushing's syndrome.

Retinoids. One woman taking an oral progestogen-only contraceptive (levonorgestrel 30 micrograms daily) showed a significant increase in plasma-progestogen while receiving *acitretin,* which indicated ovulation had occurred.[1] However, progestogen-only contraceptives do not suppress ovulation in all cycles, and this is not thought to be their primary mechanism of contraceptive efficacy (see Types of Contraceptive, p. 2231.3). Nevertheless, because it is imperative that women receiving retinoids do not conceive, some have concluded that oral progestogen-only contraceptives are not suitable for use with retinoids.[2]

The anti-ovulatory efficacy of combined oral contraceptives was not affected by acitretin in 8 women in the study above,[1] or by *etretinate* in a study[3] in 12 women. Other studies have reported that *isotretinoin* did not significantly change plasma concentrations or adversely affect contraceptive efficacy of ethinylestradiol and levonorgestrel in 9 women,[4] or ethinylestradiol and norethisterone in 26 women.[5] It has been concluded that, unless otherwise contra-indicated, oral combined contraceptives are the contraceptive method of choice for women undergoing retinoid treatment.[2] Licensed product informa-

tion for retinoids, including isotretinoin, reminds prescribers that two effective forms of contraception such as a combined oral contraceptive with a barrier method should be used during and after retinoid treatment (see also Pregnancy, under Isotretinoin, p. 1709.3).

Both isotretinoin and combined oral contraceptives can have adverse effects on plasma lipids;[6] it has therefore been recommended that plasma lipids should be monitored during concurrent retinoid and oral contraceptive therapy, and that an oral contraceptive containing a non-androgenic progestogen is preferred,[2] since these have less detrimental effects on lipids (p. 2239.2).

1. Berbis P, *et al.* Acitretin (RO10-1670) and oral contraceptives: interaction study. *Arch Dermatol Res* 1988; 280: 388–9.
2. Lehucher Ceyrac D, *et al.* Retinoids and contraception. *Dermatology* 1992; 184: 161–70.
3. Berbis P, *et al.* Study on the influence of etretinate on biologic activity of oral contraceptives. *J Am Acad Dermatol* 1987; 17: 302–3.
4. Orme M, *et al.* Isotretinoin and contraception. *Lancet* 1984; ii: 752–3.
5. Hendrix CW, *et al.* The effect of isotretinoin on the pharmacokinetics and pharmacodynamics of ethinyl estradiol and norethindrone. *Clin Pharmacol Ther* 2004; 75: 464–75.
6. Chen Y, *et al.* Elevation of serum triglyceride and cholesterol levels from isotretinoin therapy with concomitant oral contraceptives. *Pharmacoepidemiol Drug Safety* 1995; 4: 91–6.

Stimulants. *Modafinil* induces hepatic enzymes and may reduce the efficacy of oral contraceptives.[1] Licensed product information for modafinil suggests that alternative or additional methods of contraception are needed; US information recommends that this is also continued for 1 month after stopping modafinil, but in the UK it is recommended for 2 months.

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3.

1. Robertson P, *et al.* Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther* 2002; 71: 46–56.

Sugammadex. The neuromuscular blockade reverser sugammadex may bind to oestrogens and progestogens, which could decrease the efficacy of hormonal contraceptives. If a bolus dose of sugammadex is given on the same day as an oral hormonal contraceptive, the appropriate action for a missed dose of contraceptive should be taken (see Uses and Administration, p. 2231.3). If a bolus of sugammadex is given to a patient using a non-oral hormonal contraceptive, an additional non-hormonal contraceptive method should be used for the next 7 days, and the product information for the contraceptive consulted.

Vitamins. Large supplements of *vitamin C* have been reported to increase serum ethinylestradiol concentrations in women taking oral contraceptives,[1] but a further study showed no effect on either ethinylestradiol[2] or levonorgestrel.[3]

1. Back DJ, *et al.* Interaction of ethinyloestradiol with ascorbic acid in man. *BMJ* 1981; 282: 1516.
2. Zamah NM, *et al.* Absence of an effect of high vitamin C dosage on the systemic availability of ethinyl estradiol in women using a combination oral contraceptive. *Contraception* 1993; 48: 377–91.
3. Kuhnz W, *et al.* Influence of high doses of vitamin C on the bioavailability and the serum protein binding of levonorgestrel in women using a combination oral contraceptive. *Contraception* 1995; 51: 111–16.

Pharmacokinetics

For a discussion of the pharmacokinetics of oestrogens and progestogens, see Estradiol, p. 2273.3 and Progesterone, p. 2302.2, respectively. The extent of binding of progestogens to serum sex-hormone binding globulin may be altered when they are given with an oestrogen. Oestrogens increase serum concentrations of sex-hormone binding globulin, and progestogens differ in their ability to suppress this effect.

Reference to the effects of hormonal contraceptives on binding proteins.[1]

1. Fotherby K. Interactions of contraceptive steroids with binding proteins and the clinical implications. *Ann N Y Acad Sci* 1988; 538: 313–20.

Hormone Replacement Therapy

Hormonersatztherapie; HRT; THS; Traitement Hormonal Substitutif; Tratamiento hormonal restitutivo; Гормонозаместительная Терапия.

The Menopause

The menopause is defined as the permanent cessation of cyclical menstruation due to loss of ovarian follicular activity. It is therefore determined in retrospect, conventionally after 1 year without menstruation. In the few years before the menopause (the menopausal transition), ovarian oestradiol secretion declines, sometimes in a fluctuating manner, and there is a resultant increase in pituitary follicle-stimulating hormone (FSH) secretion. The menopausal transition may be characterised by irregular menstrual cycles and dysfunctional uterine bleeding, and fertility is much reduced compared with the early reproductive years. The term perimenopause is used to cover the menopausal transition and the first year after the menopause, and may last 6 years or more. It has sometimes been referred to as the climacteric. Oestrogen concentrations reach their minimum and FSH concentrations their maximum about 4 years after the menopause. After the menopause the ovaries may continue to produce some androgens; adrenal and ovarian androgens are aromatised to oestrogens (mainly oestrone) in the periphery, but oestrogen concentrations are much lower than in premenopausal women. The median age for the natural menopause is about 51 years. If the menopause occurs in women aged 40 years or less, it is considered premature. The menopause may be induced by surgical removal of both ovaries, or sometimes by antineoplastic drugs or radiotherapy.

The decline in oestrogen concentrations during the perimenopause may be associated with both acute and long-term effects. However, some of these may be difficult to differentiate from the effects of ageing, and the incidence varies geographically. Established *acute symptoms* can include vasomotor instability, manifesting as hot flushes and night sweats, and vaginal atrophy and dyspareunia. Non-specific *symptoms include* palpitations, headache, backache, and psychological symptoms such as tiredness, lack of concentration, loss of libido, irritability, insomnia, and depression. Insomnia may occur secondary to night sweats. There is little evidence that depressive illness is disproportionately increased at the menopause. Urinary problems are common in ageing women, and may occur in the perimenopause, but the extent that these are due to lack of oestrogens has not been determined. An established *long-term consequence* of the decline in oestrogen concentrations is an increased risk of bone fractures resulting from an increase in the rate of bone resorption. In addition, decline in oestrogen concentrations is associated with adverse effects on blood lipoproteins, and this may be a risk factor for cardiovascular disease.

Acute and longer-term effects of the menopause may be managed by using hormone replacement therapy (HRT) with oestrogens, with or without progestogens, and non-hormonal therapies (see Menopausal Disorders, p. 2245.1).

Uses and Administration

The term *hormone replacement therapy* (HRT) is often used to represent the use of an oestrogen, with or without a progestogen, in peri- and postmenopausal women. HRT is used for the management of acute menopausal symptoms (see p. 2245.1) such as vasomotor symptoms and atrophic vaginitis, and can be used long-term in women with premature or surgically-induced menopause until the normal age of menopause. HRT may also be used for postmenopausal osteoporosis (see p. 2246.1) in selected women, when other preferred drugs cannot be used or have been ineffective. The most commonly used oestrogens in menopausal HRT are natural oestrogens such as estradiol, and conjugated oestrogens. Dosages of oestrogens used in HRT are generally lower than those used in combined oral contraceptives, and do not therefore provide contraception.

Oestrogens for HRT are available as oral tablets, intranasal sprays, subcutaneous implants, topical applications for vulvovaginal use, intravaginal rings, and transdermal patches and gels. Generally, if prolonged therapy (for more than 2 to 4 weeks) with an oestrogen by any route is envisaged in a woman with an intact uterus, a progestogen is required to prevent endometrial proliferation. This may be given cyclically or continuously, depending on the woman's menopausal status. Cyclical regimens usually include a progestogen for 10 to 14 days of each 28-day cycle, although an extended regimen that includes a progestogen for 14 days of a 91-day cycle is also in use. Progestogens may be given orally or transdermally. Both progesterone derivatives such as medroxyprogesterone and dydrogesterone, and 19-nortestosterone analogues such as norethisterone, norgestrel, and levonorgestrel are used. Doses of progestogens for HRT are similar to those used in combined oral contraceptives.

Administration. In a discussion of the relative merits of oral and transdermal oestrogen therapy[1] it was suggested that there was circumstantial and theoretical evidence to suppose that transdermal therapy might be preferable in women who smoke, who suffer from migraine, hepatobiliary disease, or hypertriglyceridaemia, or who have a history of thromboembolism. In contrast, oral HRT might be preferable in patients with hypercholesterolaemia. However, studies to examine these suppositions were needed. Although there have been further studies comparing cardiovascular risk markers in women given oral or transdermal HRT, data on clinical outcome are scarce[2] (see also Venous Thromboembolism, under Adverse Effects, p. 2249.3). Various alternatives to oral oestrogen therapy have been reviewed.[3-5] For references and reviews about estradiol given buccally or sublingually, as implants, intranasally, or transdermally, see p. 2271.3 and p. 2272.1.

1. Lufkin EG, Ory SJ. Relative value of transdermal and oral estrogen therapy in various clinical situations. *Mayo Clin Proc* 1994; 69: 131–5.
2. Modena MG, *et al.* New evidence regarding hormone replacement therapies is urgently required: transdermal postmenopausal hormone therapy differs from oral hormone therapy in risks and benefits. *Maturitas* 2005; 52: 1–10.
3. Baker VL. Alternatives to oral estrogen replacement: transdermal patches, percutaneous gels, vaginal creams and rings, implants, and other methods of delivery. *Obstet Gynecol Clin North Am* 1994; 21: 271–97.
4. Jewelewicz R. New developments in topical estrogen therapy. *Fertil Steril* 1997; 67: 1–12.
5. Yoo J-W, Lee CH. Drug delivery systems for hormone therapy. *J Control Release* 2006; 112: 1–14.

Cardiovascular disorders. Observational studies have shown a decreased risk of ischaemic heart disease and consequent mortality in women receiving menopausal HRT and oestrogens are known to have some beneficial effects on the plasma lipid profile (see Effects on Lipids, p. 2250.1). However, results from randomised placebo-controlled studies of combined HRT for primary or secondary prevention of ischaemic heart disease have shown no overall benefit from HRT, and possibly an increased risk of coronary events (see Ischaemic Heart Disease, under Adverse Effects, p. 2248.3). It has therefore been recommended that HRT should not be used for prevention of cardiovascular disease.[1] Cardiovascular risk reduction, including management of blood lipids, is discussed on p. 1246.1.

1. Mosca L, *et al.* Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* 2004; 109: 672–93.

Dementia. Several observational studies[1-3] have suggested that oestrogens can reduce the risk and delay the onset of Alzheimer's disease (p. 388.1) in postmenopausal women receiving HRT. However, subsequent meta-analyses[4,5] concluded that studies conducted so far had substantial methodological problems and that results were conflicting. A further observational study[6] has also reported improved global cognition, and a slower rate of decline over 3 years in women receiving HRT. This study also found[7] that previous HRT use reduced the risk of developing dementia, but that current HRT use had no effect unless it was taken for more than 10 years. In contrast, another observational study (a substudy of the Nurse's Health Study[8] including 13 807 women) found no association between HRT use and cognitive performance over 2 years, and a suggestion that long-term use or initiation at older ages may increase the risk of cognitive decline. Any apparent benefits of HRT have also been thrown into question by the results of two large controlled studies of women who received conjugated oestrogens with medroxyprogesterone, or placebo, for about 4 years. At the end of the Heart and Estrogen/Progestin Replacement Study of women with coronary disease, there was no difference in cognitive function tests between those receiving HRT or placebo.[9] In the Women's Health Initiative Memory Study of over 4000 women aged 65 years and older, HRT had no clinically significant effect on global cognitive function, but the risk of suffering a substantial decline was higher for the HRT group.[10] Also, HRT did not prevent the development of mild cognitive impairment, and actually doubled the risk of dementia.[11] The absolute risk of dementia is small, however, and this increase is equivalent to 45 cases of dementia per year for every 10 000 women taking HRT compared with 22 cases for placebo. Similar effects were found for conjugated oestrogens alone in women with a prior hysterectomy who were studied in a separate arm of the Women's Health Initiative.[12,13] Pooling of data from both the oestrogen alone and combined HRT arms of this study suggested that HRT had an adverse effect on cognition,[13] increased the risk for both dementia and mild cognitive impairment, and should not be used to prevent dementia or cognitive decline.[12] A substudy of the Women's Health Initiative examined changes in specific cognitive domains, particularly memory and affect, in 1416 women given combined HRT or placebo.[14] After an average of 4 to 5 years, combined HRT had a negative effect on verbal memory, but a trend to a positive effect on figural memory; there was no significant influence on other cognitive domains and affect.

It has been suggested that age might provide an explanation for the conflict between results of observational and controlled studies. A review that compared results from controlled studies in younger women (less than 65 years old) and older women (65 or older) found that younger women may not be at risk from oestrogen alone and may benefit in verbal memory and attention.[15] However, the reviewer noted that there were limited data available on oestrogen alone in younger women and a lack of studies of combined HRT. A case-control study[16] has also reported a

reduced risk of Alzheimer's disease in younger women (50 to 63 years old), but not older women, given HRT.

Some reports[17-19] suggest that treatment with oestrogens may be of benefit in women who already have Alzheimer's disease. However, in a controlled study in women with mild to moderate Alzheimer's disease, oestrogen replacement therapy for one year did not slow the progression of disease or improve global, cognitive, or functional outcomes.[20] Further analysis of the range of hormone concentrations measured in this study[21] found no association between plasma concentrations of estradiol and estrone, and cognitive function.

1. Tang M-X, *et al.* Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996; 348: 429–32.
2. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. *Arch Intern Med* 1996; 156: 2213–17.
3. Kawas C, *et al.* A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 1997; 48: 1517–21.
4. Yaffe K, *et al.* Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998; 279: 688–95.
5. LeBlanc ES, *et al.* Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA* 2001; 285: 1489–99.
6. Carlson MC, *et al.* Hormone replacement therapy and reduced cognitive decline in older women: the Cache county study. *Neurology* 2001; 57: 2210–16.
7. Zandi PP, *et al.* Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache county study. *JAMA* 2002; 288: 2123–9.
8. Kang JH, *et al.* Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. *Neurology* 2004; 63: 101–7.
9. Grady D, *et al.* Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2002; 113: 543–8.
10. Rapp SR, *et al.* Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; 289: 2663–72.
11. Shumaker SA, *et al.* Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; 289: 2651–62.
12. Shumaker SA, *et al.* Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; 291: 2947–58.
13. Espeland MA, *et al.* Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; 291: 2959–68.
14. Resnick SM, *et al.* Women's Health Initiative Study of Cognitive Aging Investigators. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab* 2006; 91: 1802–10.
15. Maki PM. A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use. *Ann N Y Acad Sci* 2005; 1052: 182–97.
16. Henderson VW, *et al.* MIRAGE Study Group. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. *J Neurol Neurosurg Psychiatry* 2005; 76: 103–5.
17. Ohkura T, *et al.* Long-term estrogen replacement therapy in female patients with dementia of the Alzheimer type: 7 case reports. *Dementia* 1995; 6: 99–107.
18. Schneider LS, *et al.* Potential role for estrogen replacement in the treatment of Alzheimer's dementia. *Am J Med* 1997; 103 (suppl 3A): 46S–50S.
19. Asthana S, *et al.* High-dose estradiol improves cognition for women with AD: results of a randomized study. *Neurology* 2001; 57: 605–12.
20. Mulnard RA, *et al.* Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *JAMA* 2000; 283: 1007–15. Correction. *Ibid.*; 284: 2597.
21. Thal LJ, *et al.* Estrogen levels do not correlate with improvement in cognition. *Arch Neurol* 2003; 60: 209–12.

Hyperparathyroidism. The effects of HRT have been studied in postmenopausal women with mild primary hyperparathyroidism (p. 1170.3). Oestrogens have been reported to reduce the rate of bone turnover and plasma concentrations of calcium in these patients, as well as increase bone mineral density.[1-4]

1. Marcus R, *et al.* Conjugated estrogens in the treatment of postmenopausal women with hyperparathyroidism. *Ann Intern Med* 1984; 100: 633–40.
2. Selby PL, Peacock M, Ethinyl estradiol and norethindrone in the treatment of primary hyperparathyroidism in postmenopausal women. *N Engl J Med* 1986; 314: 1481–5.
3. Grey AB, *et al.* Effect of hormone replacement therapy on bone mineral density in postmenopausal women with mild primary hyperparathyroidism: a randomized, controlled trial. *Ann Intern Med* 1996; 125: 360–8.
4. Orr-Walker BJ, *et al.* Effects of hormone replacement therapy on bone mineral density in postmenopausal women with primary hyperparathyroidism: four-year follow-up and comparison with healthy postmenopausal women. *Arch Intern Med* 2000; 160: 2161–6.

Menopausal disorders. The menopause (p. 2244.1) is a natural process that occurs in women with normal ageing. For some, the only noticeable change during the perimenopause is irregular menstrual periods that eventually stop, but for others vasomotor symptoms and atrophic vaginitis can cause significant discomfort; effects vary not only between women, but also for the individual woman as she progresses through the menopausal transition. Menopausal effects can be more sudden and intense in women who have the abrupt loss of oestrogen associated with menopause induced by surgery, chemotherapy, or radiotherapy. Many reviews and guidelines have been published on management of the menopause including the use of HRT.

Acute menopausal symptoms. There are several strategies that may be tried for the management of acute menopausal symptoms.

- In postmenopausal women with only *vaginal symptoms*, non-hormonal vaginal lubricants and moisturisers can be tried first.[1] If these are inadequate, locally-acting vaginal oestrogen therapy may be effective;[1,2] improvement typically occurs within a few weeks, but may take 4 to 6 weeks. Oestrogen therapy may continue for as long as required for symptomatic relief, but data on the effects of long-term use are lacking.[1] Systemic exposure from vaginal preparations is believed to be limited, and the addition of a progestogen to protect against endometrial hyperplasia in women with a uterus is generally not indicated when low-dose local oestrogen therapy is used.[1] Nevertheless, studies have reported cases of endometrial hyperplasia and overstimulation; a systematic review found that there were insufficient data to confirm whether a progestogen should be given when vaginal oestrogens are used for more than 6 months.[2] Women using a cream may be at higher risk of systemic absorption since dosing relies on the amount of cream measured by the woman, which may be variable compared with vaginal tablets. (Some vaginal preparations are designed to deliver sufficient systemic oestrogen to treat vasomotor symptoms—see below.)
- Mild *vasomotor symptoms* may be adequately managed with lifestyle changes such as maintaining a lower core body temperature, physical activity, and relaxation techniques.[3] Moderate to severe symptoms can be controlled with HRT,[3-9] usually given orally or transdermally; some vaginal rings also deliver sufficient oestrogen to the circulation to treat vasomotor symptoms. The lowest dose that controls symptoms is given short term, generally for no more than 5 years. Women without a uterus, and who have not had endometriosis, can be given continuous oestrogen alone.[4,7,9] Women with a uterus should also receive a progestogen to reduce the risk of endometrial hyperplasia and cancer associated with unopposed oestrogen therapy[3,4,6,9] (for a discussion of the risks of endometrial cancer with HRT, see under Adverse Effects, p. 2247.3). In women who are postmenopausal (more than 12 months) continuous combined HRT may be used.[7] However, continuous combined HRT can cause irregular bleeding in perimenopausal women, so they are usually given a cyclical progestogen orally or transdermally, which will cause regular withdrawal bleeding; an alternative is the levonorgestrel intra-uterine device. Vaginal progesterone or oral long-cycle regimens (progestogen for 12 to 14 days every 3 to 6 months) have been used to reduce adverse effects, but it is not clear that these provide adequate endometrial protection.[9]

  Perimenopausal women are still potentially fertile and HRT does not provide contraception. It is now considered that women free of all risk factors for venous and arterial disease may use a low-dose combined oral contraceptive (p. 2231.3) to provide both relief of menopausal symptoms and contraception.[3] However, it is recommended that they should stop the oral contraceptive at the age of 50, so that the menstrual cycle and menopausal status can be assessed. Non-hormonal contraceptives or a progestogen-only contraceptive (see p. 2232.3) may be used if contraception is required in perimenopausal women using HRT, and continued to the age of 55 when natural sterility can be assumed.[10]

  Alternative hormonal therapies for vasomotor symptoms include the progestogens megestrol and medroxyprogesterone.[3,6,11] Tibolone, which has oestrogenic, progestogenic, and androgenic properties, is another option for postmenopausal women.[4,7,12,13]

  Non-hormonal therapies have also been tried although evidence for the efficacy of these is less conclusive than that for HRT.[3,6,11,14] The antidepressants fluoxetine, paroxetine, and venlafaxine have shown some benefit in small studies, and low doses of gabapentin have been reported to be effective. Indeed, low-dose paroxetine is used in some countries for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Clonidine or veralipride may be considered when HRT is not suitable, but the use of these can be limited by adverse effects. Other therapies have been used to manage vasomotor symptoms based on anecdotal reports of benefit, but they have generally not been effective in placebo-controlled studies. These include isoflavones from soya or red clover, evening primrose oil, cimicifuga (black cohosh), *Angelica sinensis* (dong quai), and vitamin E.
- *Non-specific symptoms* may also improve in women given HRT, but good evidence is somewhat scanty and HRT should not be used solely for these indications. Oestrogens might reduce recurrent urinary-tract infections in susceptible women,[7] but incontinence can worsen (see p. 2246.2). Many women report improved mood and well-being when given oestrogens, although it is unclear to what extent this is due to relief of other symptoms. Two large controlled studies[15,16] have found that combined HRT improved some quality of life measures in postmenopausal women with vasomotor symptoms, but that asymptomatic women in general received no benefit. There is insufficient evidence to support the use of oestrogen, alone or in combined HRT, for the treatment of depression.[9] Moreover, the addition of progestogens carries some risk of adverse effects on mood such as depression, anxiety, and irritability. Androgens such as testosterone are sometimes used as adjuncts to HRT to improve psychological well-being and libido. However, despite some evidence for efficacy in selected populations, such as surgically menopausal women, testosterone cannot be recommended for generalised use because of poorly-defined indications and a lack of evidence on long-term safety.[17]

Initiation of HRT. There is increasing discussion about when to start HRT, as the timing of treatment after menopause seems to relate to long-term health outcomes. There has been interest particularly in how the effect of HRT on ischaemic heart disease might be affected by age, considering that many women who took part in studies of HRT were older than those who generally take HRT for vasomotor symptoms in their 50s (see Ischaemic Heart Disease under Effects on the Cardiovascular System, p. 2248.3). The benefit-risk ratio is more likely to be acceptable for short-term symptomatic management in younger women around the age of typical natural menopause (about 51 years). It is also now generally advised that, unless there is a compelling indication, HRT should not be started in women older than 60 who have had a natural menopause at the typical age because they will usually have higher baseline risks of cardiovascular disease and breast cancer.[9] It is also generally agreed that all women who have had a *premature natural or induced menopause* should be offered HRT or a combined oral contraceptive until about 52 years of age, unless there are specific contra-indications to therapy. These women may need higher doses of HRT than those normally used to control vasomotor symptoms. Adjunctive androgen therapy may also be considered, particularly in oophorectomised women.[18] Considerations as to how long they need to continue HRT after the usual age for the menopause are probably the same as for other women.

Long-term use of HRT. There are extensive data from observational studies on the beneficial effects on fracture rates and cardiovascular disease, on the risks for development of breast cancer and endometrial cancer, and on the possible effects on overall mortality. However, the women receiving HRT in these studies may differ from women not receiving HRT, and the extent of any bias resulting from this is unclear.[19] Randomised prospective studies have confirmed the increased risk of breast cancer, venous thromboembolism, stroke, and dementia associated with combined HRT (see under Adverse Effects, p. 2246.3). Contrary to the anticipated benefits for preventing ischaemic heart disease, these studies also found an increase in coronary events, and such use is now not recommended (see Cardiovascular Disorders, p. 2244.3). These results have led to recommendations that HRT should not be used long term solely for the prevention of chronic disease in generally healthy postmenopausal women.[4,20,21] However, although other treatments are now preferred for the prevention and treatment of osteoporosis (p. 1168.1), long-term HRT may be suitable for some women (see also p. 2246.1).

1. North American Menopause Society. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of the North American Menopause Society. *Menopause* 2007; 14: 355–69. Also available at: http://www.menopause.org/PSvagestrogen07.pdf (accessed 23/01/08)
2. Suckling J, *et al.* Local oestrogen for vaginal atrophy in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 23/01/08).
3. Anonymous. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause* 2004; 11: 11–33. Also available at: http://www.menopause.org/Portals/0/Content/PDF/PShotflashes04.pdf (accessed 22/08/08)
4. van der Mooren MJ, Kenemans P. Postmenopausal hormone therapy: impact on menopause-related symptoms, chronic disease and quality of life. *Drugs* 2004; 64: 821–36.
5. MacLennan AH, *et al.* Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 23/01/08).
6. AACE Menopause Guidelines Revision Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. *Endocr Pract* 2006; 12: 315–37. Also available at: http://www.aace.com/pub/pdf/guidelines/menopause.pdf (accessed 23/01/08)
7. Roberts H. Managing the menopause. Abridged version: *BMJ* 2007; 334: 736–41. Correction. *Ibid.*; 335. Full version: http://www.bmj.com/cgi/content/full/334/7596/736/DC1 (accessed 23/01/08)
8. International Menopause Society. IMS updated recommendations on postmenopausal hormone therapy. *Climacteric* 2007; 10: 181–94. Also available at: http://www.imsociety.org/pdf_files/ims_recommendations/ims_updated_recommendations_on_postmenopausal_hormone_therapy_27_02_07.pdf (accessed 23/01/08)

9. North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010; 17: 242–55. Also available at: http://www.menopause.org/PSht10.pdf (accessed 20/07/10)
10. Gebbie A. Contraception in the perimenopause. *J Br Menopause Soc* 2003; 9: 123–8.
11. Fugate SE, Church CO. Nonestrogen treatment modalities for vasomotor symptoms associated with menopause. *Ann Pharmacother* 2004; 38: 1482–99.
12. Hickey M, *et al.* Treatment of menopausal symptoms: what shall we do now? *Lancet* 2005; 366: 409–21.
13. NIH State-of-the-Science Panel. National Institutes of Health State-of-the-Science conference statement: management of menopause-related symptoms. *Ann Intern Med* 2005; 142: 1003–13. Also available at: http://www.annals.org/content/142/12_Part_1/1003.full.pdf (accessed 20/07/10)
14. Nelson HD, *et al.* Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006; 295: 2057–71.
15. Hlatky MA, *et al.* Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA* 2002; 287: 591–7.
16. Hays J, *et al.* Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003; 348: 1839–54.
17. Wierman ME, *et al.* Androgen therapy in women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006; 91: 3697–3710.
18. Pitkin J, *et al.* Writing group for the British Menopause Society Council. Management of premature menopause. *Menopause Int* 2007; 13: 44–5.
19. Grodstein F, *et al.* Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med* 2003; 348: 645–50.
20. US Preventive Services Task Force. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. *Ann Intern Med* 2005; 142: 855–60. Also available at: http://www.annals.org/content/142/10/855.full.pdf (accessed 20/07/10)
21. Farquhar C, *et al.* Long term hormone therapy for perimenopausal and postmenopausal women. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2009 (accessed 19/10/09).

Osteoporosis. Oestrogens may be used in selected patients for the treatment and prevention of postmenopausal osteoporosis (p. 1168.1). They have a direct antiresorptive effect on bone, and will increase bone mass density (BMD). However, data from the Heart and Estrogen/Progestin Replacement Study (HERS) have called into question the benefit of HRT in reducing the incidence of fractures.[1,2] A meta-analysis[3] including the initial HERS data,[1] most of which were from women without osteoporosis, consequently found only non-significant reduction in fracture risk in older women although overall the risk of fracture was reduced by between 20 and 30%. Subsequent results from the Women's Health Initiative[4] showed that, contrary to the results of this meta-analysis, combined HRT did reduce the risk of fracture in healthy postmenopausal women. Similarly, cohort data from 138 737 women in the Million Women Study[5] showed that current use of HRT reduced fracture risk, but that this protection wore off rapidly after stopping HRT. Other studies have also reported that protection against loss of bone mineral density[6] and fracture[7] is not retained after stopping HRT.

Despite the probable benefits, there is substantial evidence to show that HRT is associated with an increased risk of cancer, particularly breast cancer (see Breast under Carcinogenicity, below), and some cardiovascular diseases such as stroke and venous thromboembolism (see Effects on the Cardiovascular System, p. 2248.2). It is now generally recommended by authorities, such as the UK CSM,[8] that the risk to benefit ratio of HRT is unfavourable for the prevention of osteoporosis as first-line therapy, and that it should not be used in this way for women over 50 years of age. HRT does, however, remain an option when other osteoporosis prevention therapies are unsuitable. Younger women who have undergone premature menopause may be given HRT for menopausal symptoms and to prevent osteoporosis until the age of 50, after which its use should be reviewed and considered a second-line choice.

Suggested minimum daily doses are 625 micrograms of oral conjugated oestrogens, 2 mg of oral estradiol or 50 micrograms transdermally, and 15 micrograms of oral ethinylestradiol; lower doses may also be effective,[9–15] and a transdermal patch supplying 14 micrograms of estradiol daily is licensed for the prevention of osteoporosis in the USA. Addition of a progestogen (required to prevent endometrial hyperplasia in women with a uterus) does not impair the beneficial effect of oestrogens on BMD, whether given cyclically or continuously,[16,17] and may provide a further reduction in risk of fractures.[18] Although current, long-term use of HRT can increase BMD and reduce fracture risk, unresolved issues are the duration of therapy required to prevent fractures in old age, and the ideal age to start therapy to obtain the maximum benefits to the bone with the minimum risk of breast cancer.[18–20]

Oestrogens may also be used in women to reduce the risk of corticosteroid-induced osteoporosis (see Effects on Bones and Joints, p. 1616.2).

1. Cauley JA, *et al.* Effects of hormone replacement therapy on clinical fractures and height loss: the Heart and Estrogen/Progestin Replacement Study (HERS). *Am J Med* 2001; 110: 442–50.
2. Hulley S, *et al.* Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; 288: 58–66.
3. Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001; 285: 2891–7.
4. Cauley JA, *et al.* Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003; 290: 1729–38.
5. Banks E, *et al.* Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA* 2004; 291: 2212–20.
6. Greendale GA, *et al.* Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. *Arch Intern Med* 2002; 162: 665–72.
7. Yates J, *et al.* Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. *Obstet Gynecol* 2004; 103: 440–6.
8. MHRA. Further advice on safety of HRT: risk:benefit unfavourable for first-line use in prevention of osteoporosis—Epinet message from Professor G Duff, Chairman of CSM (issued December 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019496.pdf (accessed 26/08/08)
9. Recker RR, *et al.* The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women: a randomized, controlled trial. *Ann Intern Med* 1999; 130: 897–904.
10. Prestwood KM, *et al.* The effect of low dose micronized 17 β -estradiol on bone turnover, sex hormone levels, and side effects in older women: a randomized, double blind, placebo-controlled study. *J Clin Endocrinol Metab* 2000; 85: 4462–9.
11. Bjarnason NH, *et al.* Low doses of estradiol in combination with gestodene to prevent early postmenopausal bone loss. *Am J Obstet Gynecol* 2000; 183: 550–60.
12. Lees B, Stevenson JC. The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17 β and dydrogesterone. *Osteoporosis Int* 2001; 12: 251–8.
13. Lindsay R, *et al.* Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA* 2002; 287: 2668–76.
14. Prestwood KM, *et al.* Ultralow-dose micronized 17 β -estradiol and bone density and bone metabolism in older women: a randomized controlled trial. *JAMA* 2003; 290: 1042–8.
15. Lindsay R, *et al.* Bone response to treatment with lower doses of conjugated estrogens with and without medroxyprogesterone acetate in early postmenopausal women. *Osteoporosis Int* 2005; 16: 372–9.
16. The Writing Group for the PEPI trial. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. *JAMA* 1996; 276: 1389–96.
17. Speroff L, *et al.* The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART Study): a randomized controlled trial. *JAMA* 1996; 276: 1397–1403.
18. Michaëlsson K, *et al.* Hormone replacement therapy and risk of hip fracture: population based case-control study. *BMJ* 1998; 316: 1858–63.
19. Schneider DL, *et al.* Timing of postmenopausal estrogen for optimal bone mineral density: the Rancho Bernardo study. *JAMA* 1997; 277: 543–7.
20. Cauley JA, *et al.* Timing of estrogen replacement therapy for optimal osteoporosis prevention. *J Clin Endocrinol Metab* 2001; 86: 5700–5.

Urinary incontinence. Urinary incontinence (p. 2349.2) may be one of several acute symptoms associated with a decline in oestrogen levels at the menopause (see Menopausal Disorders, p. 2245.1). Studies[1,2] suggest that oestrogens used with alpha-adrenoceptor agonists are effective in the management of female stress incontinence and this combination has been advocated for use in postmenopausal patients with mild symptoms. Unfortunately addition of a progestogen to treatment to reduce the risk of endometrial carcinoma in women with an intact uterus might exacerbate the incontinence.[3] The value of oestrogens used without an alpha-adrenoceptor agonist in urinary incontinence is less clear. One study[4] reported that oestrogen therapy and pelvic floor exercises for 18 months was more effective than exercises alone in women with mild stress incontinence. However, a placebo-controlled study[5] found no improvement after 6 months of oestrogen therapy.

Some consider that oestrogens may be of use for symptoms of urgency, frequency, and nocturia in postmenopausal patients with urge incontinence, particularly if given locally;[6] it has been suggested that hypoestrogenism may reduce the sensory threshold of the bladder.[7] A meta-analysis of 23 studies concluded that oestrogen therapy subjectively improved urinary incontinence in postmenopausal women but many of the studies examined were considered to be deficient in some respect.[8] Later well-designed studies[9,10] of women with stress, urge, or mixed incontinence found that HRT did not improve, or even worsened, measures of incontinence, although there was the possibility that concomitant progestogen therapy might have affected efficacy. Furthermore, the placebo-controlled Women's Health Initiative[11] found that both oestrogen alone and combination HRT increased the overall risk of developing stress, urge, or mixed incontinence, and worsened incontinence in women who were symptomatic before starting HRT. Another placebo-controlled study[12] also found that combination HRT increased the risk of developing stress or urge incontinence, and the large Nurses' Health Study cohort reported[13] that the current use of HRT increased the risk of developing urinary incontinence.

1. Walter S, *et al.* Stress urinary incontinence in postmenopausal women treated with oral estrogen (estriol) and an alpha-adrenoceptor-stimulating agent (phenylpropanolamine): a randomized double-blind placebo-controlled study. *Int Urogynecol J* 1990; 1: 74–9.
2. Hilton P, *et al.* Oral and intravaginal estrogens alone and in combination with alpha-adrenergic stimulation in genuine stress incontinence. *Int Urogynecol J* 1990; 1: 80–6.
3. Benness C, *et al.* Do progestogens exacerbate urinary incontinence in women on HRT? *Neurourol Urodyn* 1991; 10: 316–17.
4. Ishiko O, *et al.* Hormone replacement therapy plus pelvic floor muscle exercise for postmenopausal stress incontinence: a randomized, controlled trial. *J Reprod Med* 2001; 46: 213–20.
5. Jackson S, *et al.* The effect of oestrogen supplementation on postmenopausal urinary stress incontinence: a double-blind placebo-controlled trial. *Br J Obstet Gynaecol* 1999; 106: 711–18.
6. Cardozo L, *et al.* A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. *Acta Obstet Gynecol Scand* 2004; 83: 892–7.
7. Fantl JA, *et al.* Postmenopausal urinary incontinence: comparison between non-estrogen-supplemented and estrogen-supplemented women. *Obstet Gynecol* 1988; 71: 823–8.
8. Fantl JA *et al.* Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis: first report of the hormones and urogenital therapy committee. *Obstet Gynecol* 1994; 83: 12–18.
9. Fantl JA, *et al.* Efficacy of estrogen supplementation in the treatment of urinary incontinence. *Obstet Gynecol* 1996; 88: 745–9.
10. Grady D, *et al.* Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. *Obstet Gynecol* 2001; 97: 116–20.
11. Hendrix SL, *et al.* Effects of estrogen with and without progestin on urinary incontinence. *JAMA* 2005; 293: 935–48.
12. Steinauer JE, *et al.* The Heart and Estrogen/Progestin Replacement Study Research Group. Postmenopausal hormone therapy: does it cause incontinence? *Obstet Gynecol* 2005; 106: 940–5.
13. Grodstein F, *et al.* Postmenopausal hormone therapy and risk of developing urinary incontinence. *Obstet Gynecol* 2004; 103: 254–60.

Adverse Effects of HRT

When oestrogens are used for menopausal HRT, adverse effects include nausea and vomiting, abdominal cramps and bloating, weight changes, breast enlargement and tenderness, premenstrual-like syndrome, sodium and fluid retention, altered blood lipids, cholestatic jaundice, glucose intolerance, rashes and chloasma (melasma), changes in libido, migraine, dizziness, depression, mood changes, headache, leg cramps, vaginal candidiasis, and decreased tolerance of contact lenses. Transdermal delivery systems may cause contact sensitisation (possibly severe hypersensitivity reactions on continued exposure), and nasal sprays may cause local irritation, rhinorrhoea, and epistaxis. Headache has been reported on vigorous exercise. Use of oestrogen without a progestogen results in endometrial hyperplasia and an increased risk of endometrial carcinoma (see p. 2247.3). The addition of a progestogen for 10 to 14 days of a 28-day cycle reduces this risk but results in regular withdrawal bleeding towards the end of the progestogen. Use of continuous progestogen and oestrogen avoids withdrawal bleeding, but may result in irregular breakthrough bleeding, particularly in the early stages of therapy, or if used within 12 months of the last menstrual period. Current use of menopausal HRT is associated with an increased risk of venous thromboembolism and breast cancer (see p. 2249.3 and below).

Reviews.

1. Winship KA. Unopposed oestrogens. *Adverse Drug React Acute Poisoning Rev* 1987; 1: 37–66.
2. Evans MP, *et al.* Hormone replacement therapy: management of common problems. *Mayo Clin Proc* 1995; 70: 800–5.

Carcinogenicity. Use of unopposed oestrogen as menopausal HRT in women with a uterus increases the risk of endometrial cancer, irrespective of the route of administration. This risk is reduced, although possibly not eliminated completely, by the concomitant use of a progestogen. There is also evidence that use of HRT, as oestrogen alone or with a progestogen, increases the risk of breast cancer.

Because of continuing modifications in regimens for HRT there is a continuing need to monitor the incidence of various cancers in users of this therapy.

The carcinogenicity of combined menopausal HRT has been reviewed.[1]

1. IARC/WHO. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. *IARC monographs on the evaluation of carcinogenic risks to humans volume 91* 2007. Available at: http://monographs.iarc.fr/ENG/Monographs/vol91/mono91.pdf (accessed 20/07/10)

BREAST. Early age at menarche and late age at menopause increase the risk of breast cancer, and surgical oophorectomy at an early age decreases the risk of breast cancer. In addition, higher concentrations of unbound endogenous oestrogens in postmenopausal women appear to increase the risk of developing breast cancer.[1] Such risk factors have prompted concerns that menopausal HRT might be associated with an increased risk of breast cancer.

Reviews and analyses[2–4] of studies published during the 1970s and/or 1980s on the use of **unopposed oestrogen** replacement therapy in postmenopausal women have generally shown that there is an associated moderate increase in the risk of breast cancer; figures for overall relative risk compared with non-oestrogen users ranged from under 1 to up to 2. One of these,[3] a meta-analysis of studies from 1976 to 1989, further showed that although the relative risk of breast cancer rose to 1.3 after 15 years of oestrogen use, it did not appear to rise at all until after 5 years of use. A similar meta-analysis[4] differentiated between low-dose oestrogens and high-dose oestrogens; those taking

625 micrograms daily of conjugated oestrogens had a risk of breast cancer 1.08 times higher than non-oestrogen users, whereas the relative risk in those taking 1.25 mg daily or more was up to 2.0. A subsequent meta-analysis[5] differentiated between current use of HRT, duration of use, and use at any time. The highest relative risk of breast cancer was associated with current use (1.4); use for 10 years or more was associated with a relative risk of about 1.2, and having ever used HRT was not associated with an increased risk. In 1997 the Collaborative Group on Hormonal Factors in Breast Cancer reanalysed about 90% of the worldwide evidence on breast cancer and the use of HRT.[6] They reported that the relative risk of having breast cancer diagnosed was increased by a factor of 1.023 for each year of use, being 1.35 for 5 or more years of use. However, this effect was reduced on cessation of use, and had largely disappeared after about 5 years. In women who started therapy at age 50, the cumulative excess number of breast cancers diagnosed per 1000 women between age 50 and 70 were estimated to be 2, 6, and 12 for 5, 10, and 15 years of use, respectively, from a baseline of 45 per 1000 in never-users.[6] In contrast, the arm of the Women's Health Initiative[7] that compared conjugated oestrogens with placebo over an average of about 7 years found a trend towards a reduction in breast cancer risk with HRT. A Finnish cohort study[8] also found no increase in risk with less than 5 years of oral estradiol or estriol therapy. For women taking unopposed oestrogen in the Nurses' Health Study[9] cohort the linear increase in risk with increasing duration of use did not become statistically significant until current use exceeded 20 years.

Most data relate to the use of unopposed oestrogen. There has been speculation both that the concomitant use of progestogen in HRT could reduce the risk of breast cancer and that it might increase it. Bergkvist *et al.*[10] suggested an increased relative risk of 4.4 in the small subgroup using long-term **combined therapy**, but because of the large confidence intervals they considered these results inconclusive. Analysis of the Nurses' Health Study cohort has provided evidence that current use of oestrogen and progestogen is associated with a similar increased relative risk of breast cancer to that of unopposed oestrogen (1.4 versus 1.3).[11] The Collaborative Group on Hormonal Factors in Breast Cancer[6] found no evidence of marked differences between preparations containing oestrogens alone and those containing oestrogens and progestogens. However, in a randomised study, oestrogen plus progestogen was associated with greater increases in radiographic breast density than unopposed oestrogen.[12] The results of further cohort studies[13,14] and case-control studies[15,16] also suggest that the risk of breast cancer may be higher for current or recent use of combined HRT compared with oestrogen alone, and a cohort study[17] of over 1 million women (the Million Women Study) found relative risks of 1.3 for users of oestrogen alone, and 2.0 for combined HRT, compared with never-users. After an average follow-up of about 5 years the Women's Health Initiative,[18] comparing combined HRT with placebo in more than 16 000 women, was stopped early because of an increased rate of invasive breast cancer in women given HRT.

The public health perspective on the implications of any increased risk of breast cancer will depend on the background risk. This is high in western countries, so a small increased relative risk would equate to a large absolute increase in number of cases.[19]

If menopausal oestrogen therapy increases the risk of breast cancer, there is a need to ascertain whether these cancers can be detected early, how aggressive they are, and what the mortality rate from them is. Currently, there are limited data on these points.

- There is evidence[20,21] that the use of HRT decreases the sensitivity and specificity of screening mammography (resulting in more false positives and more false negatives), apparently because it increases radiographic breast density[22,23] or slows the natural change from dense patterns to fatty patterns,[24] so decreasing the ability to interpret the mammogram. This is of concern for the success of screening programmes, and has been suggested as a factor in the increased detection of interval cancers (those detected between screening appointments).[25] In addition, HRT-associated increases in radiographic breast density could actually be a marker for risk of breast cancer.[12,26]
- Some data suggest that breast cancers in women on HRT may be of better prognostic grade.[27,28] The Collaborative Group on Hormonal Factors in Breast Cancer reported that breast cancers were more likely to be localised in current or recent users of HRT, but that there was evidence of an increased risk of metastasis with increasing duration of use.[6] However, the Women's Health Initiative[26] did not confirm previous findings of favourable prognosis, and found breast cancers in combined HRT users to be larger, more likely to be node positive, and at a more advanced stage at diagnosis. The likelihood of good prognostic grade in women on HRT may depend on the histological type of any lesion that develops: invasive lobular and tubular cancers are more strongly associated with current use of HRT than invasive ductal cancer.[29]
- Follow-up of most studies is currently insufficient to give a clear indication of mortality risk with long-term use. Early data from a UK cohort study[30] suggested a decreased risk of breast cancer mortality, but after further follow-up the risk was no longer reduced.[31] Similarly, a study in 2614 women with breast cancer followed up for up to 22 years found that the use of HRT at the time of diagnosis was associated with a reduction in mortality, but the effect waned over time.[32] In contrast, data[11] from the Nurses' Health Study cohort suggest an increase in risk of death from breast cancer in women who have currently used HRT for 5 years or more (1.45). Similarly, although mortality was lower overall, a trend towards an increased risk of death from breast cancer (1.9; 95% confidence interval 0.4 to 8.4) was seen in a study of long-term use (mean of 17 years).[33]

The risk of breast cancer may be increased further by the use of HRT in women who are already at an increased risk. Although a study found a modest increase in risk in these women, it was not significantly higher, and there was a reduced total mortality rate.[34] It is unclear whether use of HRT in breast cancer survivors increases the risk of subsequent recurrence and associated mortality (see also Malignant Neoplasms under Precautions, p. 2250.2).

1. Toniolo PG, *et al.* A prospective study of endogenous estrogens and breast cancer in postmenopausal women. *J Natl Cancer Inst* 1995; 87: 190–7.
2. Henderson BE. The cancer question: an overview of recent epidemiologic and retrospective data. *Am J Obstet Gynecol* 1989; 161: 1859–64.
3. Steinberg KK, *et al.* A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. *JAMA* 1991; 265: 1985–90.
4. Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer. *Arch Intern Med* 1991; 151: 67–72.
5. Colditz GA, *et al.* Hormone replacement therapy and risk of breast cancer: results from epidemiologic studies. *Am J Obstet Gynecol* 1993; 168: 1473–80.
6. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997; 350: 1047–59. Correction. *ibid.*: 1484.
7. Stefanick ML, *et al.* Women's Health Initiative Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006; 295: 1647–57.
8. Lyytinen H, *et al.* Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol* 2006; 108: 1354–60.
9. Chen WY, *et al.* Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med* 2006; 166: 1027–32.
10. Bergkvist L, *et al.* The risk of breast cancer after estrogen and estrogen–progestin replacement. *N Engl J Med* 1989; 321: 293–7.
11. Colditz GA, *et al.* The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995; 332: 1589–93.
12. Greendale GA, *et al.* Effects of estrogen and estrogen-progestin on mammographic parenchymal density. *Ann Intern Med* 1999; 130: 262–9.
13. Schairer C, *et al.* Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000; 283: 485–91.
14. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from The Nurses' Health Study. *Am J Epidemiol* 2000; 152: 950–64.
15. Ross RK, *et al.* Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000; 92: 328–32.
16. Li CI, *et al.* Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA* 2003; 289: 3254–63.
17. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419–27. Correction. *ibid.*: 1160.
18. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321–33.
19. WHO. Research on the menopause in the 1990s: report of a WHO scientific group. *WHO Tech Rep Ser 866* 1996. Also available at: http://libdoc.who.int/trs/WHO_TRS_866.pdf (accessed 24/01/08)
20. Laya MB, *et al.* Effect of estrogen replacement therapy on the specificity and sensitivity of screening mammography. *J Natl Cancer Inst* 1996; 88: 643–9.
21. Kavanagh AM, *et al.* Hormone replacement therapy and accuracy of mammographic screening. *Lancet* 2000; 355: 270–4.
22. Rutter CM, *et al.* Changes in breast density associated with initiation, discontinuation, and continuing use of hormone replacement therapy. *JAMA* 2001; 285: 171–6.
23. McTiernan A, *et al.* Women's Health Initiative Mammogram Density Study Investigators. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. *J Natl Cancer Inst* 2005; 97: 1366–76.
24. van Duijnhoven FJB, *et al.* Postmenopausal hormone therapy and changes in mammographic density. *J Clin Oncol* 2007; 25: 1323–8.
25. Cohen EL. Effect of hormone replacement therapy on cancer detection by mammography. *Lancet* 1997; 349: 1624.
26. Chlebowski RT, *et al.* Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA* 2003; 289: 3243–53.
27. Harding C, *et al.* Hormone replacement therapy and tumour grade in breast cancer: prospective study in screening unit. *BMJ* 1996; 312: 1646–7. Correction. *ibid.*: 313: 198.
28. Gapstur SM, *et al.* Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. *JAMA* 1999; 281: 2091–7.
29. Reeves GK, *et al.* Million Women Study Collaborators. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol* 2006; 7: 910–18.
30. Hunt K, *et al.* Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. *Br J Obstet Gynaecol* 1987; 94: 620–35.
31. Hunt K, *et al.* Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. *Br J Obstet Gynaecol* 1990; 97: 1080–6.
32. Schairer C, *et al.* Estrogen replacement therapy and breast cancer survival in a large screening study. *J Natl Cancer Inst* 1999; 91: 264–70.
33. Ettinger B, *et al.* Reduced mortality associated with long-term postmenopausal estrogen therapy. *Obstet Gynecol* 1996; 87: 6–12.
34. Sellers TA, *et al.* The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. *Ann Intern Med* 1997; 127: 973–80.

CERVIX. Studies of the effect of HRT on cervical cancer risk are likely to be subject to the potential confounding of other risk factors such as sexual activity. There are few data on this risk; one study[1] suggested oestrogens do not increase, and may decrease, the risk of cervical cancer, but another[2] suggested that unopposed oestrogen might increase the risk of adenocarcinoma. Therapy with combined HRT did not significantly affect the incidence of cytological abnormalities found in annual cervical smears in women in the Heart and Estrogen/progestin Replacement Study (HERS).[3] In the Women's Health Initiative study,[4] however, there was an overall increase in the incidence of new abnormalities in women given combined HRT, compared with placebo, although the incidence of high-grade squamous intra-epithelial lesion and cervical cancer was not affected.

1. Parazzini, F, *et al.* Case-control study of oestrogen replacement therapy and risk of cervical cancer. *BMJ* 1997; 315: 85–8.
2. Lacey JV, *et al.* Use of hormone replacement therapy and adenocarcinomas and squamous cell carcinomas of the uterine cervix. *Gynecol Oncol* 2000; 77: 149–54.
3. Sawaya GF, *et al.* The positive predictive value of cervical smears in previously screened postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS). *Ann Intern Med* 2000; 133: 942–50.
4. Yasmeen S, *et al.* Incidence of cervical cytological abnormalities with aging in the Women's Health Initiative: a randomized controlled trial. *Obstet Gynecol* 2006; 108: 410–19.

ENDOMETRIUM. The increased incidence of endometrial hyperplasia and risk of cancer in women receiving unopposed oestrogen replacement therapy is well established. An analysis of case control studies published during the 1970s and 1980s revealed a relative risk of developing endometrial cancer of 1.4 to 7.6 in women who had ever used oestrogen, and a relative risk of 3.1 to 15 in long-term users, compared with nonusers.[1] Risk was also increased with higher doses of oestrogens. In general, endometrial cancer in oestrogen users was of a better prognostic stage, and survival rates were better, than in nonusers.[1] An elevated risk of endometrial cancer persists for several years after stopping unopposed oestrogen therapy.[2]

Addition of a progestogen to oestrogen replacement therapy reduces the incidence of endometrial hyperplasia[3] and cancer. However, the extent to which this alters the risks and benefits of oestrogen replacement therapy, and the optimum progestogen type, and dose and duration, have not been fully elucidated.

As regards risk of endometrial cancer, preliminary data from a cohort study revealed that the addition of cyclical progestogen to oestrogen therapy reduced this risk compared with oestrogen therapy alone.[4] A further case-control study confirmed that progestogens decreased the relative risk, and that the reduction in risk was greater when progestogens were used for 10 or more days per month than when they were used for less than 10 days per month.[5] Two much larger case-control studies have confirmed these findings.[6,7] However, 1 of these studies[6] reported that in long-term users the addition of a progestogen did not reduce the risk of endometrial cancer to that seen in nonusers—after 5 years of use, the relative risk of endometrial cancer with HRT containing 10 or more days of progestogen per month was 2.5 (95% confidence intervals 1.1 to 5.5). This finding remains to be confirmed.

Use of progestogens for 10 days of an 84-day cycle (long cycle) has been suggested to improve acceptability of combined HRT. However, one study of a long-cycle regimen was stopped because of an increased risk of endometrial hyperplasia and atypia compared with a conventional monthly cycle regimen.[8]

Some newer regimens of HRT use continuous low doses of progestogen with oestrogen, which avoid withdrawal bleeding. Data on the incidence of endometrial hyperplasia from randomised studies of these regimens have been reassuring.[3,9,10] Continuous norethisterone plus ethinylestradiol,[9] and continuous medroxyprogesterone plus conjugated oestrogens,[10] protected the endometrium against the hyperplasia seen with the oestrogen alone. In comparing continuous and sequential regimens of combined oral HRT, a meta-analysis[3] suggested that they were associated with similar risks of endometrial hyperplasia, but the sequential regimens that had been studied were quite varied and there were insufficient data available to adequately compare different regimens. The first data on endometrial cancer risk from continuous combined HRT suggest that it is as protective as sequential therapy with the progestogen given

for 10 or more days per month (odds ratio 1.07 per 5 years of use for both regimens).[7] The Women's Health Initiative reported[11] that although the rate of endometrial cancer for continuous combined HRT was reduced, it was not significantly different to placebo over 5 years. However, in the analysis of endometrial cancer in the Million Women cohort study,[12] in which 55% of the 716738 women had not used HRT, there was a lower risk of endometrial cancer with continuous combined HRT, whereas it was not altered for cyclic combined HRT, and was higher for oestrogen-only HRT and tibolone. The beneficial effects of combined HRT were also found to be greatest in obese women.

It is unclear whether use of HRT in endometrial cancer survivors increases the risk of subsequent recurrence and associated mortality (see also Malignant Neoplasms under Precautions, p. 2250.2).

1. Henderson BE. The cancer question: an overview of recent epidemiologic and retrospective data. *Am J Obstet Gynecol* 1989; 161: 1859–64.
2. Rubin GL, *et al.* Estrogen replacement therapy and the risk of endometrial cancer: remaining controversies. *Am J Obstet Gynecol* 1990; 162: 148–54.
3. Furness S, *et al.* Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 20/07/10).
4. Persson I, *et al.* Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: results of a prospective study. *BMJ* 1989; 298: 147–51.
5. Voigt LF, *et al.* Progestagen supplementation of exogenous oestrogens and risk of endometrial cancer. *Lancet* 1991; 338: 274–7.
6. Beresford S, *et al.* Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet* 1997; 349: 458–61.
7. Pike MC, *et al.* Estrogen-progestin replacement therapy and endometrial cancer. *J Natl Cancer Inst* 1997; 89: 1110–16.
8. Cerin A, *et al.* Adverse endometrial effects of long-cycle estrogen and progestogen replacement therapy. *N Engl J Med* 1996; 334: 668–9.
9. Speroff L, *et al.* The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART Study). *JAMA* 1996; 276: 1397–1403.
10. The Writing Group for the PEPI trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. *JAMA* 1996; 275: 370–5.
11. Anderson GL, *et al.* Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003; 290: 1739–48.
12. Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005; 365: 1543–51.

GASTROINTESTINAL TRACT. Evidence of an effect of oestrogen replacement therapy on colorectal cancer is ambiguous, since studies have reported both an increased and a decreased incidence; a meta-analysis in 1995 suggested no overall effect.[1] However, subsequent cohort studies did suggest a lower incidence of colon cancer in those who had received oestrogens.[2,3] This was most pronounced in current users in whom the relative risk was about one-third to one-half of that for women who had never taken oestrogen. Similarly, a large case-control study also reported a significant reduction in colon cancer, but not rectal cancer.[4] A later meta-analysis[5] concluded that the risk of colon cancer might be decreased among women who have recently used HRT, and that the risk of death from colon cancer might also be reduced. The Women's Health Initiative,[6] a placebo-controlled study of combined HRT in more than 16000 women, found that those taking HRT had a decreased risk of developing colorectal cancer, but that at diagnosis there was greater lymph node involvement and it was at a more advanced stage.

There is less information on the effect of HRT on death from colorectal cancer. In the Nurses' Health Study cohort[7] there were decreased risks of death from colorectal cancer and death overall for women taking HRT when cancer was diagnosed, compared with those who had never taken HRT. However, this benefit was limited to women who had been taking HRT for no more than 5 years before diagnosis; longer duration of use and past use had no effect on survival.

1. MacLennan SC, *et al.* Colorectal cancer and oestrogen replacement therapy: a meta-analysis of epidemiological studies. *Med J Aust* 1995; 162: 491–3.
2. Calle EE, *et al.* Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst* 1995; 87: 517–23.
3. Grodstein F, *et al.* Postmenopausal hormone use and risk for colorectal cancer and adenoma. *Ann Intern Med* 1998; 128: 705–12.
4. Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. *J Natl Cancer Inst* 1995; 87: 1067–71.
5. Nanda K, *et al.* Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol* 1999; 93: 880–8.
6. Chlebowski RT, *et al.* Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004; 350: 991–1004.
7. Chan JA, *et al.* Hormone replacement therapy and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006; 24: 5680–6.

OVARY. There was no clear evidence that the use of oestrogen replacement therapy altered the risk of invasive ovarian cancer in various case-control studies reviewed by the Collaborative Ovarian Cancer Group.[1] However, subsequent study of a large cohort has suggested that long-term oestrogen replacement therapy may increase the risk of fatal ovarian cancer.[2,3] Similarly, a meta-analysis indicated an increased risk for invasive epithelial ovarian cancer, especially after long-term use of HRT.[4] Another, later, cohort study[5] also reported that there was an increased risk of ovarian cancer with oestrogen replacement therapy, particularly when given for 10 years or more, but found no increase for combined HRT. A Swedish case-control study[6] looked at different types of HRT and also found that the risk was increased with oestrogen replacement therapy. For combined HRT, however, the risk was increased for women who had used sequential combined HRT (continuous oestrogen plus cyclical progestogen), but not for those who had used continuous combined HRT. Similarly, in the Women's Health Initiative,[7] a placebo-controlled study of continuous combined HRT in more than 16000 women, the increased incidence of ovarian cancer was not significant during 5.6 years of follow-up. Further cohort data support an association with long-term current use of unopposed oestrogen replacement therapy,[8-10] but the role of progestogen remains less clear; the Million Women Study[10] also found increased risks with combined HRT, but the Nurses' Health Study[9] found no association. In the cohort NIH-AARP Diet and Health Study[8] the risk of ovarian cancer was also increased overall for 5 or more years of combined HRT use, and found to be higher for users of sequential compared with continuous combined HRT.

1. Whittemore AS, *et al.* Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. *Am J Epidemiol* 1992; 136: 1184–1203.
2. Rodriguez C, *et al.* Estrogen replacement therapy and fatal ovarian cancer. *Am J Epidemiol* 1995; 141: 828–35.
3. Rodriguez C, *et al.* Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001; 285: 1460–5.
4. Garg PP, *et al.* Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. *Obstet Gynecol* 1998; 92: 472–9.
5. Lacey JV, *et al.* Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 2002; 288: 334–41. Correction. *ibid.*: 2544.
6. Riman T, *et al.* Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J Natl Cancer Inst* 2002; 94: 497–504.
7. Anderson GL, *et al.* Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003; 290: 1739–48.
8. Lacey JV, *et al.* Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. *J Natl Cancer Inst* 2006; 98: 1397–1405.
9. Danforth KN, *et al.* A prospective study of postmenopausal hormone use and ovarian cancer risk. *Br J Cancer* 2007; 96: 151–6.
10. Million Women Study Collaborators. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2007; 369: 1703–10.

Effects on carbohydrate metabolism. Data from a survey of postmenopausal women showed that diabetic women who were currently taking HRT had better glycaemic control than those who had never taken HRT or were previous users.[1] In the Heart and Estrogen/Progestin Replacement study[2] in postmenopausal women with ischaemic heart disease, there was no significant change in fasting glucose concentrations after 4 years of combined HRT in women with or without diabetes compared with a rise in women given placebo. There was also a lower risk of developing diabetes in those given HRT (cumulative incidence 6.2%) compared with placebo (9.5%). The Women's Health Initiative study[3] reported changes in fasting glucose and insulin concentrations, indicating a fall in insulin resistance, in women treated with combined HRT. During an average 5.6 years of follow-up there was a lower incidence of diabetes in women given HRT (3.5%) compared with placebo (4.2%). This represented an absolute reduction of 15 cases of treated diabetes per 10000 women per year of HRT treatment.

Although HRT may improve glycaemic control in diabetic postmenopausal women, it is generally used with caution in this group. Diabetic patients are already at increased risk of cardiovascular disease, and HRT may be associated with an increased risk of ischaemic heart disease (see below).

1. Crespo CJ, *et al.* Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care* 2002; 25: 1675–80.
2. Kanaya AM, *et al.* Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003; 138: 1–9.
3. Margolis KL, *et al.* Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004; 47: 1175–87.

Effects on the cardiovascular system. Various facts support the theory that endogenous oestrogens may be cardioprotective. For example, mortality rates for cardiovascular disease in women are lower than those in men at all ages. In addition, women who have a surgically induced menopause at a young age are at increased risk of ischaemic heart disease compared with women who have a natural menopause.

Conversely, use of high doses of oestrogens for malignant disease is associated with an increased risk of cardiovascular events. Similarly, use of oestrogens in combined oral contraceptives carries a small increased risk of cardiovascular disease (see p. 2237.1). Moreover, an early study in men surviving a myocardial infarction found that high doses of conjugated oestrogens (5 mg daily) were associated with a higher incidence of subsequent coronary events than placebo (see Effects on the Cardiovascular System, in Conjugated Oestrogens, p. 2260.3).

In practice, some large observational studies found a decreased risk of ischaemic heart disease and mortality in women receiving menopausal HRT compared with those who have never received this therapy (see below). The reduction in risk was estimated as 30 to 50%, but biases such as the healthy user effect seem to play a part in this estimate; unfortunately, results from controlled studies have cast doubt on the extent of any reduction in risk. There is also evidence to show that HRT *increases* the risk of stroke (see p. 2249.2) and venous thromboembolism (see p. 2249.3).

The mechanisms by which oestrogen exerts its cardiovascular effects are not fully understood.[1] Oestrogen has beneficial effects on lipoproteins, but adverse effects on triglycerides (see p. 2250.1). Similarly, it has beneficial effects on some, and adverse effects on other, mediators of thrombosis. Oestrogen may also have a direct beneficial effect on the coronary vasculature. Progestogens may reduce the beneficial effects of oestrogens on some lipids, although observational data has suggested that this is not sufficient to reverse potential benefit.

1. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999; 340: 1801–11.

HYPERTENSION. Although high doses of oestrogens have been associated with increased blood pressure, use of menopausal HRT in normotensive and hypertensive women has little effect on blood pressure or may be associated with a small decrease.[1-4] An observational study[5] of normotensive postmenopausal women also found that, over time, the average increase in systolic blood pressure was significantly less in women who were taking HRT.

1. Affinito P, *et al.* Effects of hormonal replacement therapy in postmenopausal hypertensive patients. *Maturitas* 2001; 40: 75–83.
2. Mueck AO, Seeger H. Effect of hormone therapy on BP in normotensive and hypertensive postmenopausal women. *Maturitas* 2004; 49: 189–203.
3. Steiner AZ, *et al.* Postmenopausal oral estrogen therapy and blood pressure in normotensive and hypertensive subjects: the Estrogen in the Prevention of Atherosclerosis Trial. *Menopause* 2005; 12: 728–33.
4. Karalis I, *et al.* Hormone replacement therapy and arterial blood pressure in postmenopausal women with hypertension. *Blood Pressure* 2005; 14: 38–44.
5. Scuteri A, *et al.* Hormone replacement therapy and longitudinal changes in blood pressure in postmenopausal women. *Ann Intern Med* 2001; 135: 229–38.

ISCHAEMIC HEART DISEASE. In 1991, Stampfer and Colditz reviewed 31 case-control and cohort studies on the risk of ischaemic heart disease in women using menopausal HRT.[1] Four studies showed an adverse trend, 2 showed no effect on risk, and 25 showed a trend to reduction in risk or a significant reduction in risk. The summary relative risk was 0.56, with estimated 95% confidence intervals of 0.50 to 0.61. Other reviews have reported similar reductions in risk.[2,3] Much of the data relate to the use of unopposed oestrogen, which is no longer recommended in women with a uterus because of the risk of endometrial cancer (see p. 2247.3).

There was concern that the **addition of progestogen** might negate or reduce the cardiovascular benefits of oestrogens by reducing the oestrogen-induced rise in serum high-density-lipoprotein cholesterol concentrations. It was postulated that this might be particularly true for progestogens derived from nortestosterone rather than progesterone. Results from the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) indicated that the beneficial effects on blood lipoproteins and fibrinogen, although greatest with unopposed oestrogen, were still present when combined with medroxyprogesterone or micronised progesterone (micronised progesterone was preferable to medroxyprogesterone).[4] Moreover, the UK Medical Research Council Study reported a fairly even balance between possibly beneficial and adverse effects on lipid concentrations and coagulability when conjugated oestrogens alone were compared with conjugated oestrogens plus norgestrel (a nortestosterone derivative).[5] Similar results were reported in the CHART study for ethinylestradiol with or without norethisterone.[6] Although reassuring, these 3 studies provided information only on surrogate endpoints.

Data from the Nurses' Health Study cohort[7] showed a greater reduction in the risk of major ischaemic heart disease among women receiving an oestrogen plus a progestogen (relative risk 0.4) than those receiving an oestrogen alone (0.6), as compared with the risk in women not using hormones. *In-vitro* data suggest that progestogens may actually protect against atherosclerosis via inhibition of smooth muscle cell proliferation.[8]

As regards **duration of HRT use**, current use appeared to be the most important factor for cardiovascular risk reduction. Users with coronary risk factors appeared to derive greater benefit from HRT than those at low risk of coronary artery disease.[9] Of concern, the Nurses' Health Study reported that the apparent benefit from HRT

decreased with increasing duration of use beyond 10 years because of an increase in mortality from breast cancer.[9]

However, a number of studies have now found no beneficial effect on risk of heart disease. In contrast to previous findings, a retrospective case-control study[10] did not find a decreased risk of myocardial infarction in women currently using combined HRT or oestrogens alone. The authors of this study suggested that the benefit of HRT may not be as large as has been estimated in some qualitative overviews, and emphasised the need for data from randomised studies.[10] This has been confirmed by results[11] of the Heart and Estrogen/Progestin Replacement Study, a randomised placebo-controlled study in women with established ischaemic heart disease. Combined HRT with conjugated oestrogens plus medroxyprogesterone produced no overall reduction in the occurrence of myocardial infarction or death due to ischaemic heart disease in these women. This overall lack of effect was due to an initial increase in cardiac events during the first year, with a later beneficial effect in years 3 to 5. During unblinded follow-up[12] of 2.7 years, these late beneficial effects did not persist and the risk of cardiovascular events was not reduced. Observational data from the Nurses' Health Study cohort[13] also noted a trend towards an initial increase in cardiac events followed by a decrease in risk with long-term use of HRT, in women with a history of ischaemic heart disease. Other studies found that HRT did not affect the progression of existing coronary atherosclerosis as measured by angiography.[14,15] Oestrogen therapy for 2 years also had no effect on the risk of further cardiac events in postmenopausal women who had survived a myocardial infarction.[16] There is also some evidence that the risks and benefits of HRT may vary according to the presence or absence of particular prothrombotic mutations.[17]

These worrying results have suggested that HRT should not be used for secondary prevention in women with heart disease, in contrast to some earlier suggestions (see also Cardiovascular Disorders under Uses and Administration, p. 2244.3).

In women without pre-existing heart disease, observational data from the Nurses' Health Study[18] showed a reduced risk of major coronary events in users of HRT, compared with never-users. However, there were increased rates of coronary events at an average follow-up of about 5 years in the Women's Health Initiative,[19] a primary prevention study comparing combined HRT with placebo in over 16 000 women. The risk was highest in the first year of HRT but decreased to a smaller non-significant excess risk in the following years.[20] The arm of the Women's Health Initiative that compared unopposed conjugated oestrogens with placebo in more than 10 000 women with prior hysterectomy found that over an average of 7 years there was no difference in the risk of ischaemic heart disease.[21,22] These results suggest that HRT should also not be used for primary prevention of ischaemic heart disease.

There is continuing debate about the effect of HRT on ischaemic heart disease, and how it might be influenced by age. The generalisability of some study results, such as in the Women's Health Initiative, has been questioned because the mean age of the study group has been much older than women who generally take HRT for vasomotor symptoms in their 50s. A meta-analysis[23] has compared data from younger and older women, and found that for younger women (less than 10 years since menopause or under 60 years of age) there was a reduced risk of myocardial infarction or cardiac death with HRT. In older women, however, events increased in the first year then decreased after 2 years, resulting in a neutral effect over time. Secondary analysis[24] of the Women's Health Initiative data found that for women who started HRT closer to menopause (aged 50 to 59 years or less than 10 years since menopause) there was a trend towards reduced risks of ischaemic heart disease and death, while risk increased with age and time since menopause. One factor might be the reduction by HRT of atherosclerotic calcification in the coronary arteries.[25] Further studies are underway to examine the effect of HRT, started soon after menopause, in the prevention of atherosclerosis.

1. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991; 20: 47–63.
2. Grady D, *et al.* Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992; 117: 1016–37.
3. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. *JAMA* 1991; 265: 1861–7.
4. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995; 273: 199–208. Correction. *ibid.*; 274: 1676.
5. Medical Research Council's General Practice Research Framework. Randomised comparison of oestrogen versus oestrogen plus progestogen hormone replacement therapy in women with hysterectomy. *BMJ* 1996; 312: 473–8.
6. Speroff L, *et al.* The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART Study): a randomized controlled trial. *JAMA* 1996; 276: 1397–1403.
7. Grodstein F, *et al.* Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; 335: 453–61. Correction. *ibid.*; 1046.
8. Lee W-S, *et al.* Progesterone inhibits arterial smooth muscle cell proliferation. *Nature Med* 1997; 3: 1005–1008.
9. Grodstein F, *et al.* Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997; 336: 1769–75.
10. Sidney S, *et al.* Myocardial infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. *Ann Intern Med* 1997; 127: 501–8.
11. Hulley S, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; 280: 605–13.
12. Grady D, *et al.* Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; 288: 49–57. Correction. *ibid.*; 1064.
13. Grodstein F, *et al.* Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study: a prospective, observational study. *Ann Intern Med* 2001; 135: 1–8.
14. Herrington DM, *et al.* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000; 343: 522–9.
15. Hodis HN, *et al.* Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003; 349: 535–45.
16. The ESPRIT team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002; 360: 2001–8.
17. Psaty BM, *et al.* Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. *JAMA* 2001; 285: 906–13.
18. Grodstein F, *et al.* A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; 133: 933–41.
19. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321–33.
20. Manson JE, *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003; 349: 523–34.
21. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291: 1701–12.
22. Rsia J, *et al.* Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006; 166: 357–65.
23. Salpeter SR, *et al.* Coronary heart disease events associated with hormone therapy in younger and older women. *J Gen Intern Med* 2006; 21: 363–6.
24. Rossouw JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; 297: 1465–77. Correction. *ibid.* 2008; 299: 1426.
25. Manson JE, *et al.* WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007; 356: 2591–2602.

STROKE. The Framingham Study suggested a more than twofold increased risk of stroke in women using menopausal HRT.[1] However, subsequent studies reporting risk of stroke separately from other cardiovascular events showed either no effect on risk[2] or a decreased risk in the order of 30 to 50%.[3,4]

Data from the Nurses' Health Study cohort[5] revealed little association between the risk of stroke of any type and current use of unopposed oestrogens or oestrogen plus progestogen. However, they reported a trend towards an increased risk of stroke in current users of high-dose oestrogen therapy (1.25 mg or higher). Similarly, a large Danish case-control study found that unopposed oestrogens or oestrogen plus progestogen had no effect on the risk of non-fatal haemorrhagic or thromboembolic stroke,[6] and data from the Heart and Estrogen/Progestin Replacement Study indicated that combined HRT in women with pre-existing ischaemic heart disease had no effect on risk of stroke.[7,8] In contrast to these results, the Women's Health Initiative, a placebo-controlled study of over 16 000 healthy women, found that combined HRT increased the risk of ischaemic stroke, and that the increase in risk became apparent after about 1 year of starting HRT.[9] Furthermore, the arm of the Women's Health Initiative that compared unopposed conjugated oestrogens with placebo in more than 10 000 women with prior hysterectomy also found an increased risk of stroke;[10] additional data and analysis also confirmed that the increased risk was for ischaemic stroke, and appeared after about 4 years.[11] Although the numbers of haemorrhagic strokes were small in both Women's Health Initiative studies, the combined data showed no significant effect of hormone therapy.[11] A systematic review,[12] which was dominated by the results of the Women's Health Initiative, found that HRT was associated with an increase in stroke. This was attributed largely to ischaemic stroke, whereas there was no significant change in the risks of haemorrhagic stroke, fatal stroke, or transient ischaemic attack. A poor outcome (death or dependency) was also found to be more likely with HRT. Secondary analysis[13] of the Women's Health Initiative data also found that the risk of stroke was increased regardless of years since menopause.

In a controlled study in postmenopausal women who had recently had a stroke or transient ischaemic attack, the use of unopposed oestrogen had no significant effect on mortality or the recurrence of stroke.[14]

1. Wilson PWF, *et al.* Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: the Framingham study. *N Engl J Med* 1985; 313: 1038–43.
2. Stampfer MJ, *et al.* Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med* 1991; 325: 756–62.
3. Paganini-Hill A, *et al.* Postmenopausal oestrogen treatment and stroke: a prospective study. *BMJ* 1988; 297: 519–22.
4. Finucane FF, *et al.* Decreased risk of stroke among postmenopausal hormone users: results from a national cohort. *Arch Intern Med* 1993; 153: 73–9.
5. Grodstein F, *et al.* Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; 335: 453–61. Correction. *ibid.*; 1406.
6. Tønnes Pedersen A, *et al.* Hormone replacement therapy and risk of non-fatal stroke. *Lancet* 1997; 350: 1277–83.
7. Simon JA, *et al.* Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001; 103: 638–42.
8. Grady D, *et al.* Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; 288: 49–57. Correction. *ibid.*; 1064.
9. Wassertheil-Smoller S, *et al.* Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003; 289: 2673–84.
10. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291: 1701–12.
11. Hendrix SL, *et al.* Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006; 113: 2425–34.
12. Bath PMW, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005; 330: 342–4.
13. Rossouw JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; 297: 1465–77. Correction. *ibid.* 2008; 299: 1426.
14. Viscoli CM, *et al.* A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001; 345: 1243–9.

VENOUS THROMBOEMBOLISM. Traditionally it has been assumed that, unlike combined oral contraceptives, menopausal HRT is not associated with an increased risk of venous thromboembolism.

However, observational studies have provided substantial evidence that there is an increased risk of deep-vein thrombosis and/or pulmonary embolism in women receiving HRT.[1-4] The relative risk of venous thromboembolism was found to be 2.1 to 3.6 in current users compared with past-users or those who had never received HRT. This equates to an excess of 16 to 23 cases per 100 000 women per year. One study found that the increase in risk was restricted to the first year of use.[4] Another reported an increased risk with increasing oestrogen dose.[2]

Evidence from later randomised placebo-controlled studies[5-8] supports the findings of the observational studies above. Results from the Women's Health Initiative also suggest that the risk is higher with combined HRT than oestrogen alone.[9] It has been suggested that transdermal HRT might be preferable in women with a history of thromboembolism (see Administration, p. 2244.2) and a case-control study[10] reported that unlike oral preparations, transdermal oestrogen was not associated with an increased risk of venous thromboembolism.

The UK CSM considers that the absolute risk of venous thromboembolism in all women using HRT is higher than was originally suggested, and that the risks are higher particularly in older women and in women with predisposing factors, such as a history of venous thromboembolism.[11] Women with the factor V Leiden thrombophilia are at high risk of developing venous thromboembolism when taking HRT. The pooled results of 2 studies showed[12] that in the presence of this thrombophilia alone the odds ratio of developing venous thromboembolism was 3.58, and for HRT alone was 3.16, but women who had both these risk factors had a much higher risk of 13.16.

1. Daly E, *et al.* Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996; 348: 977–80.
2. Jick H, *et al.* Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996; 348: 981–83.
3. Grodstein F, *et al.* Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet* 1996; 348: 983–7.
4. Pérez Gutthann S, *et al.* Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997; 314: 796–800.
5. Grady D, *et al.* Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2000; 132: 689–96. Correction. *ibid.* 2001; 134: 81.
6. Hulley S, *et al.* Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; 288: 58–66.
7. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321–33.
8. Cushman M, *et al.* Women's Health Initiative Investigation. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004; 292: 1573–80.
9. Curb JD, *et al.* Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006; 166: 772–80.
10. Canonico M, *et al.* Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007; 115: 840–5.
11. CSM/MCA. New product information for hormone replacement therapy. *Current Problems* 2002; 28: 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074546&RevisionSelectionMethod=LatestReleased (accessed 23/01/08)
12. Wu O, *et al.* Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost* 2005; 94: 17–25.

Effects on the eyes. The risk of dry eye increases with age, when tear production normally decreases. The incidence is

higher in women, but it is unclear whether sex hormone changes in perimenopausal and postmenopausal women play a role in ocular surface dysfunction.[1] The effects of HRT on the incidence and management of dry eye have been debated. Relief of symptoms has occurred in some women given HRT[1] and improvements in tests of tear function and conjunctival epithelium have been reported.[2] However, a large cohort study[3] found a higher prevalence of dry eye syndrome in women taking HRT, particularly oestrogen alone, than in those not taking HRT.

1. Versura P, Campos EC. Menopause and dry eye: a possible relationship. *Gynecol Endocrinol* 2005; **20**: 289–98.
2. Pelit A, *et al.* Tear function tests and conjunctival impression cytology before and after hormone replacement therapy in postmenopausal women. *Eur J Ophthalmol* 2003; **13**: 337–42.
3. Schaumberg DA, *et al.* Hormone replacement therapy and dry eye syndrome. *JAMA* 2001; **286**: 2114–19.

Effects on the gallbladder. The use of HRT is reported to increase the risk of gallstone formation and cholecystectomy in postmenopausal women.[1-4]

1. Uhler ML, *et al.* Estrogen replacement therapy and gallbladder disease in postmenopausal women. *Menopause* 2000; **7**: 162–7.
2. Simon JA, *et al.* Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2001; **135**: 493–501.
3. Hulley S, *et al.* Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288**: 58–66.
4. Cirillo DJ, *et al.* Effect of estrogen therapy on gallbladder disease. *JAMA* 2005; **293**: 330–9.

Effects on lipids. Oestrogens increase serum high-density-lipoprotein cholesterol and decrease low-density-lipoprotein cholesterol concentrations, effects that are considered favourable and may be a mechanism behind their apparent reduction in ischaemic heart disease in postmenopausal women, although controlled studies have not found combined HRT to reduce coronary events (see Effects on the Cardiovascular System, p. 2248.2). Oestrogens may also increase serum triglyceride concentrations, which is undesirable. Severe hypertriglyceridaemia and pancreatitis have occurred in women with hypertriglyceridaemia treated with oestrogens.[1,2] Use of concomitant progestogen reduces oestrogen-induced hypertriglyceridaemia.[2]

1. Glueck CJ, *et al.* Severe hypertriglyceridemia and pancreatitis when estrogen replacement therapy is given to hypertriglyceridemic women. *J Lab Clin Med* 1994; **123**: 59–64.
2. Isley WL, Oki J. Estrogen-induced pancreatitis after discontinuation of concomitant medroxyprogesterone therapy. *Am J Med* 1997; **102**: 416–17.

Effects on mental function. For results suggesting that HRT may increase the risk of developing dementia see under Uses and Administration, p. 2244.3.

Effects on the pancreas. Unopposed oestrogen has been associated with pancreatitis in women with hypertriglyceridaemia (see Effects on Lipids, above). There have also been a few cases of pancreatitis, attributed to HRT, in which triglyceride concentrations were within the normal range.[1,2]

1. Blake WED, Pitcher ME. Estrogen-related pancreatitis in the setting of normal plasma lipids: case report. *Menopause* 2003; **10**: 99–101.
2. Trenque-Tessereau M-GB, *et al.* Combined estradiol/gestodene and acute pancreatitis. *Ann Pharmacother* 2005; **39**: 1953–4.

Precautions

Before menopausal HRT is given the woman should undergo an appropriate medical examination and her medical history should be carefully evaluated. Regular examination is recommended during use.

HRT should be avoided in women with active thrombophlebitis or thromboembolic disease; it should not be given to those with a history of recurrent thromboembolism unless they are already receiving anticoagulant treatment.

HRT should not be given to those with undiagnosed abnormal vaginal bleeding, and abnormal vaginal bleeding during therapy should be investigated (see p. 2251.1). HRT is also contra-indicated in women with oestrogen-dependent neoplasms such as those of the breast or endometrium, and is usually considered contra-indicated in women with a history of these conditions although this has been debated (see below). Active liver disease and Dubin-Johnson or Rotor syndromes are also generally considered to be contra-indications.

Prolonged exposure to unopposed oestrogens increases the risk of endometrial cancer whatever the route of administration (see p. 2247.3); they must not be given to women with untreated endometrial hyperplasia. HRT should be used with caution in women with antiphospholipid antibodies or predisposing factors to thromboembolism (see also Venous Thromboembolism, p. 2249.3), and in gallbladder disease, migraine, a history of breast nodules or fibrocystic disease, uterine fibroids, or a history of endometriosis. HRT should also be used with caution in women with diabetes because of the increased risk of heart disease. Consideration should be given to temporarily stopping HRT 4 to 6 weeks before elective surgery (but see also below).

HRT should be stopped immediately, and appropriate investigations and treatment carried out, if any of the following occur:

- sudden severe chest pain, sudden breathlessness, or severe pain/swelling in calf of one leg (possibly indicative of thromboembolic complications)
- unusual, severe, prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body, or other signs or symptoms suggestive of cerebrovascular accident
- a first unexplained epileptic seizure
- hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain
- significant rise in blood pressure (above 160 mmHg systolic or 95 mmHg diastolic)
- clear exacerbation of other conditions known to be capable of deteriorating during HRT or pregnancy.

Although evidence is in many cases less well established, HRT should perhaps also be used with caution in diseases that may be exacerbated during pregnancy or oestrogen therapy including asthma, epilepsy, hypertension, renal disease, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and SLE.

Doses of oestrogen in HRT are insufficient to provide contraception. HRT is contra-indicated in known or suspected pregnancy, and in women who are breast feeding.

Endometriosis. Women with endometriosis who are treated with hysterectomy and bilateral oophorectomy undergo a surgically-induced menopause and can have acute menopausal symptoms; they are also at risk of conditions such as osteoporosis from long-term oestrogen deficiency. HRT until about 50 years of age has been recommended for women who undergo premature menopause, but disease reactivation and malignant transformation to adenocarcinoma in residual foci have been reported in women with a history of endometriosis, particularly with unopposed oestrogen. Although there are limited data to quantify the risks from HRT, they appear to be small. Nevertheless, recurrent disease may be more severe, with a greater chance of causing ureteric obstruction and consequent renal damage. To minimise the risks of reactivation and malignancy, women with a history of endometriosis should probably be given continuous combined HRT at the lowest effective dose. Although witholding HRT for a few months to wait for endometriosis to regress after surgery has been recommended, there is limited supporting evidence and others suggest that HRT may be started soon after surgery.[1]

1. Soliman NP, Hillard TC. Hormone replacement therapy in women with past history of endometriosis. *Climacteric* 2006; **9**: 325–35.

Lupus erythematosus. SLE is an auto-immune disease which is far more common in women than in men, and usually has a peak onset for women in their 20s and 30s. There is some evidence to suggest that menopausal HRT use may be associated with a slightly increased risk in the onset of SLE in older women.[1-3] In women with pre-existing SLE, small studies found no apparent effect of HRT on disease flares.[2] In a larger study of 351 women, who were given either combined HRT or placebo for 12 months, severe flares were rare in both groups but mild to moderate flares were increased in the HRT group.[4]

Women with SLE are at increased risk of thromboembolic disease, and it has been suggested that transdermal oestrogen HRT may have less of a thrombogenic effect than oral HRT.[5] Women with antiphospholipid antibodies (which includes about a third of all patients with SLE) are at the highest risk and some[5] suggest that HRT should be avoided altogether in patients with persistent antibodies.

1. Petri M. Exogenous estrogen in systemic lupus erythematosus: oral contraceptives and hormone replacement therapy. *Lupus* 2001; **10**: 222–6.
2. Mok CC, *et al.* Use of exogenous estrogens in systemic lupus erythematosus. *Semin Arthritis Rheum* 2001; **30**: 426–35.
3. Costenbader KH, *et al.* Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007; **56**: 1251–62.
4. Buyon JP, *et al.* The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann Intern Med* 2005; **142**: 953–62.
5. Gompel A, Plette JC. Systemic lupus erythematosus and hormone replacement therapy. *Menopause Int* 2007; **13**: 65–70.

Malignant neoplasms. HRT is usually avoided in women who have been treated for *breast cancer* because of the concern that oestrogen will stimulate cancer recurrence. A retrospective observational study[1] and a retrospective case-control study[2] among women diagnosed with breast cancer did not find any evidence of an adverse effect in those who began HRT after diagnosis. A systematic review[3] of studies of HRT in breast cancer survivors reached a similar conclusion, but also noted that these studies were small, not randomised, and many were uncontrolled. More recently, an open randomised study[4] was stopped early when it was found that 2 years of HRT increased the risk of breast cancer (local recurrence, contralateral cancer, or distant metastases); this has cast doubt on the safety of HRT in these patients. A similar study, however, found that about 4 years of HRT did not increase the risk of cancer recurrence.[5] Comparing these two results, the authors suggested that the increased risk may have been due to the use of combined HRT that included continuous progestogen, rather than cyclic or long-cycle regimens. A systematic review[6] of 20 studies, including these two, highlighted the many differences in design such as HRT regimens used, and concluded that in the absence of sufficient evidence of safety HRT should not be used in women with a history of breast cancer. Other reviewers[7] have also recommended a cautious approach, suggesting that HRT should not be used for first-line management of menopausal symptoms in these women, but may be justified when other treatments have failed. The safety of different HRT regimens requires further study.[6,7]

Similarly, HRT is usually avoided in patients who have been treated for *endometrial cancer*, because of the theoretical risk of stimulating tumour recurrence.[8] There is a lack of well-designed studies on this subject, but some data suggest that HRT might not increase the rate of recurrence or death.[9,10]

Women who carry *mutations of the BRCA1 and BRCA2 genes* are at greatly increased risk of breast and ovarian cancers, and prophylactic oophorectomy after child-bearing may be considered as a means of reducing this risk. The use of HRT to manage the subsequent menopausal symptoms has been controversial because of concerns that it may adversely affect the risk of breast cancer. One study[11] that used a decision analytical model concluded that HRT did not negate the benefits of oophorectomy; the degree of life expectancy loss or gain was relatively small and influenced by length of HRT use, age at oophorectomy, and presence or absence of concurrent mastectomy. The authors suggested that the decision to use short-term HRT should be based on quality of life issues rather than life expectancy, and that HRT should be stopped at or before the expected age of natural menopause. A subsequent cohort study[12] also found that the use of HRT did not negate the protective effect of prophylactic oophorectomy against breast cancer in BRCA1/2 mutation carriers. Despite these reassuring results, data are limited and further studies are needed to determine appropriate formulations and the optimal timing and duration of HRT for these women.[13]

1. Durna EM, *et al.* Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. *Med J Aust* 2002; **177**: 347–51.
2. O'Meara ES, *et al.* Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst* 2001; **93**: 754–62.
3. Col NF, *et al.* Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol* 2001; **19**: 2357–63.
4. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet* 2004; **363**: 453–5.
5. von Schoultz E, *et al.* Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst* 2005; **97**: 533–5.
6. Antoine C, *et al.* Safety of hormone therapy after breast cancer: a qualitative systematic review. *Hum Reprod* 2007; **22**: 616–22.
7. Hickey M, *et al.* Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncol* 2005; **6**: 687–95.
8. Committee on Gynecologic Practice. ACOG committee opinion: hormone replacement therapy in women treated for endometrial cancer (number 235, May 2000). *Int J Gynecol Obstet* 2001; **73**: 283–4.
9. Suriano KA, *et al.* Estrogen replacement therapy in endometrial cancer patients: a matched control study. *Obstet Gynecol* 2001; **97**: 555–60.
10. Barakat RR, *et al.* Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2006; **24**: 587–92.
11. Armstrong K, *et al.* Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. *J Clin Oncol* 2004; **22**: 1045–54.
12. Rebbeck TR, *et al.* Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005; **23**: 7804–10.
13. Rubinstein WS. Surgical management of BRCA1 and BRCA2 carriers: bitter choices slightly sweetened. *J Clin Oncol* 2005; **23**: 7772–4.

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

The *BNF* suggests that progestogens should be avoided whenever possible, but that oestrogens may be safe in replacement doses. The risk of an acute attack is greatest in women who have had a previous attack or are under 30 years of age. Long-acting progestogen preparations should never be used in those at risk.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/10/13)

Surgery. A review[1] recommended that women receiving HRT and due to have major elective surgery or leg surgery should continue taking the HRT and should routinely

receive thromboprophylaxis (e.g. subcutaneous low-molecular-weight heparins and the use of graduated elastic compression stockings) in the perioperative period. Similar management was proposed when undergoing emergency surgery but prophylaxis was considered unnecessary with minor surgery. These conclusions were based on the advice of specialist groups but it was noted that there was some conflict with recommendations in licensed product information and those of the *BNF* at that time.

The *BNF* currently states that it may be prudent to stop HRT 4 to 6 weeks before major surgery; failing that, prophylaxis as above is recommended. HRT should only be restarted after full mobilisation.

1. Anonymous. Drugs in the peri-operative period: hormonal contraceptives and hormone replacement therapy. *Drug Ther Bull* 1999; 37: 78–80.

Vaginal bleeding. Menopausal HRT is contra-indicated in patients with undiagnosed abnormal vaginal bleeding, which may be a symptom of endometrial carcinoma. The causes of abnormal vaginal bleeding in women receiving HRT and guidelines on their investigation and treatment have been reviewed.[1-3]

1. Good AB. Diagnostic options for assessment of postmenopausal bleeding. *Mayo Clin Proc* 1997; 72: 345–9.
2. Spencer CP, *et al.* Management of abnormal bleeding in women receiving hormone replacement therapy. *BMJ* 1997; 315: 37–42.
3. Oehler MK, *et al.* Assessment of abnormal bleeding in menopausal women: an update. *J Br Menopause Soc* 2003; 9: 117–21.

Withdrawal. Although it is now generally recommended that menopausal HRT used to relieve vasomotor and vaginal symptoms should be given at the lowest effective dose for no longer than necessary (see Menopausal Disorders, p. 2245.1), there has been little study of how to effectively withdraw HRT without a recurrence of menopausal symptoms. When the Women's Health Initiative (WHI) study was stopped prematurely, the effect of HRT withdrawal was assessed in 8405 of the women in this study who were receiving either combined HRT or placebo at the time.[1] A range of menopausal symptoms were reported in both groups. Moderate to severe vasomotor symptoms (hot flushes and night sweats) occurred in 21.2% of women who stopped HRT, compared with 4.8% stopping placebo; younger women were more likely to develop symptoms. Pain and stiffness was reported by about 37% who stopped HRT, with a similar incidence across age groups. Having these symptoms at study entry was the strongest factor for recurrence when treatment ended.

Once the WHI study was stopped, many other women were also advised, or independently chose, to stop HRT; retrospective studies in smaller groups have reported the recurrence of troublesome menopausal symptoms in 30% or more.[2-4] There also appeared to be no advantage to tapering the withdrawal of HRT, compared with stopping abruptly.[2,3] Women reported using various measures to manage recurrent menopausal symptoms,[1,3,4] including lifestyle management such as exercise and drinking more fluids, vaginal oestrogen therapy, antidepressants, and preparations such as cimicifuga (black cohosh), soya, or red clover; in some cases women restarted HRT.

1. Ockene JK, *et al.* Symptom experience after discontinuing use of estrogen plus progestin. *JAMA* 2005; 294: 183–93.
2. Grady D, *et al.* Predictors of difficulty when discontinuing postmenopausal hormone therapy. *Obstet Gynecol* 2003; 102: 1233–9.
3. Haskell SG. After the Women's Health Initiative: postmenopausal women's experiences with discontinuing estrogen replacement therapy. *J Womens Health (Larchmt)* 2004; 13: 438–42.
4. Ness J, *et al.* Menopausal symptoms after cessation of hormone replacement therapy. *Maturitas* 2006; 53: 356–61.

Interactions

Drugs that increase the hepatic metabolism of oestrogens and progestogens have been associated with failure of the combined oral contraceptive (see p. 2242.3). Important examples include rifamycins and some antiepileptics. It is not unreasonable to assume that these drugs would also be associated with decreased efficacy of HRT, but there appears to be little information on this (for one report, see Antiepileptics, below).

Although oral contraceptives alter the effects of many drugs (see p. 2242.3), the lower doses of oestrogens used in HRT are considered less likely to induce interactions, although the possibility remains.

A study[1] in 12 healthy women aged 20 to 25 years, using bupropion as a probe reaction, found that HRT (estradiol valerate with levonorgestrel) was an inhibitor of the cytochrome P450 isoenzyme CYP2B6.

1. Palovaara S, *et al.* Inhibition of cytochrome P450 2B6 activity by hormone replacement therapy and oral contraceptive as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2003; 74: 326–33.

Alcohol. Acute ingestion of an alcoholic beverage led to a threefold increase in circulating estradiol in a study of women on menopausal HRT.[1] Another study[2] that included 309 women taking HRT found that about half had low serum-estradiol concentrations, and that moderate alcohol consumption was one of the factors associated with achieving therapeutic concentrations.

Both alcohol consumption and HRT are risk factors for breast cancer, and cohort studies[3,4] have suggested that the risk from the combination may be higher than the individual risks alone.

1. Ginsburg ES, *et al.* Effects of alcohol ingestion on estrogens in postmenopausal women. *JAMA* 1996; 276: 1747–51.
2. Gavaler JS. Oral hormone replacement therapy: factors that influence the estradiol concentrations achieved in a multiracial study population. *J Clin Pharmacol* 2002; 42: 137–44.
3. Chen WY, *et al.* Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Ann Intern Med* 2002; 137: 798–804.
4. Zhang SM, *et al.* Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol* 2007; 165: 667–76.

Antiepileptics. *Phenytoin* was reported to reduce the effect of conjugated oestrogens in a menopausal woman.[1]

1. Notelovitz M, *et al.* Interaction between estrogen and Dilantin in a menopausal woman. *N Engl J Med* 1981; 304: 788–9.

Levothyroxine. Increased doses of levothyroxine may be needed in hypothyroid women who receive oestrogens for postmenopausal HRT—see p. 2342.2.

Melatonin. For the effect of oestrogens on melatonin, see p. 2552.2.

Vitamins. The effect of oral *ascorbic acid* (500 mg twice daily) on plasma concentrations of estradiol was studied in 25 postmenopausal women stabilised on transdermal estradiol gel.[1] After 1 month, estradiol concentrations had risen for the group overall by about 21%. The greatest responses were in those who initially had low plasma concentrations of ascorbic acid or estradiol. The authors suggested that the antioxidant effect of ascorbic acid might reverse the oxidation of oestrogens, but that these results did not support the general use of ascorbic acid as an adjuvant to HRT.

1. Vihtamäki T, *et al.* Oral ascorbic acid increases plasma oestradiol during postmenopausal hormone replacement therapy. *Maturitas* 2002; 42: 129–35.

Pharmacokinetics

For a discussion of the pharmacokinetics of oestrogens and progestogens, see Estradiol, p. 2273.3 and Progesterone, p. 2302.2, respectively. The extent of binding of progestogens to serum sex-hormone binding globulin may be altered when they are given with an oestrogen. Oestrogens increase serum concentrations of sex-hormone binding globulin, and progestogens differ in their ability to suppress this effect.

Gonad-regulating Hormones

The Hypothalamic-Pituitary-Gonadal Axis

The regulation of sexual function involves the so-called hypothalamic-pituitary-gonadal axis.

The pituitary gland or hypophysis is composed in humans of 2 parts, the anterior lobe or adenohypophysis, and the posterior lobe (neurohypophysis) and neural stalk, above which lies the hypothalamus. Both parts of the pituitary secrete hormones: posterior pituitary hormones are synthesised in the hypothalamus and transported down nerve fibres to the pituitary where they are stored until required, whereas anterior pituitary hormones are synthesised *in situ* by specialised cells, but are subject to complex hormonal control by hypothalamic regulatory hormones and target organ hormones, as well as excitatory and inhibitory impulses from the brain. These interacting systems are collectively known as the hypothalamic-pituitary-endocrine axes.

The anterior pituitary hormones follicle-stimulating hormone (FSH) and luteinising hormone (LH) are collectively known as **gonadotrophic hormones** or gonadotrophins. They are glycoproteins secreted by specialised pituitary cells (gonadotropes) that stimulate gonadal function and sex hormone production. In men, LH stimulates the synthesis of testosterone and other androgens, while in women, FSH and LH regulate production of oestradiol and synthesis of progesterone in a complex and interacting manner. A third substance with gonadotrophic (mainly luteinising) actions, chorionic gonadotrophin, is secreted by the placenta.

The synthesis and secretion of pituitary gonadotrophic hormones is in turn stimulated by a hypothalamic releasing hormone, **gonadotrophin-releasing hormone** (GnRH). In post-pubertal subjects, GnRH is secreted from the hypothalamus at regular intervals determined by an internal 'clock' or neuronal pulse generator in the arcuate nucleus, and enters the blood of the portal vascular system that links the hypothalamus to the anterior pituitary. This results in pulsatile release of the gonadotrophic hormones, which is essential for normal gonadal function. More prolonged and continuous exposure to GnRH leads to desensitisation and downregulation of its receptors on pituitary gonadotropes, and hence, after an initial surge, to suppression of gonadotrophic hormone secretion.

The sex hormones themselves produce negative feedback effects at both hypothalamic and pituitary levels. In general, both oestrogen and progesterone reduce the amplitude (i.e. the amount) of gonadotrophic hormone released; progesterone also reduces the frequency of the pulses. Testosterone is thought to act by conversion to oestrogen via aromatase, although it also has some direct action. The gonads also produce a hormone, inhibin, that selectively inhibits FSH secretion from the pituitary without affecting LH, and its biological opposite, activin, which stimulates pituitary FSH secretion.

Types of Gonad-regulating Hormone

Gonad-regulating hormones in clinical use may be divided into 3 major groups.

- Endogenous follicle-stimulating and luteinising hormones are available from urinary sources as human menopausal gonadotrophins (p. 2284.1) or menotrophin (p. 2284.1) and as urofollitropin (p. 2312.2), and in recombinant forms such as follitropins alfa (p. 2278.2) and beta (p. 2278.2) and lutropin alfa (p. 2287.1). Chorionic gonadotrophin (p. 2258.1) and its recombinant form choriogonadotropin alfa (p. 2258.1) are also used.
- The hypothalamic releasing hormone gonadorelin (p. 2280.2), and its longer-acting analogues such as buserelin (p. 2256.2), deslorelin (p. 2266.3), goserelin (p. 2282.3), histrelin (p. 2283.3), leuprorelin (p. 2285.3), nafarelin (p. 2292.2), and triptorelin (p. 2310.3) are widely used to stimulate or inhibit the hypothalamic-pituitary-gonadal axis.
- More recently, direct gonadotrophin-releasing hormone antagonists have become available, such as abarelix (p. 2255.1), cetrorelix (p. 2257.2), and ganirelix (p. 2279.2).

Use of Gonad-regulating Hormones

The gonad-regulating hormones play an important role in the management of particular endocrine disorders, as discussed in the reviews below and elsewhere in this chapter. They also play an important role in the management of endocrine-sensitive malignant neoplasms (see p. 691.2).

Amenorrhoea

Amenorrhoea is the absence or abnormal cessation of menstruation whereas oligomenorrhoea is infrequent and erratic periods. Amenorrhoea occurring from the time of puberty is known as primary, while amenorrhoea developing later in life is referred to as secondary. Primary amenorrhoea is generally investigated when menstruation has not started by 15 years of age in the presence of normal secondary sexual development, or within 5 years after breast development if that occurred before age 10. Secondary amenorrhoea lasting 3 months, and oligomenorrhoea involving less than 9 cycles a year, should be investigated in women who have had regular menstrual cycles and are not pregnant, lactating, or menopausal. Pathological amenorrhoea is usually associated with infertility (see also p. 2253.1). Hirsutism (p. 2262.1) may also be present.

The causes of amenorrhoea or oligomenorrhoea are most often ovarian or hypothalamic/pituitary in origin. Ovarian causes include failure of normal gonadal development, as in Turner's syndrome (p. 2254.3); premature ovarian failure including that due to trauma, drugs, radiotherapy, or autoimmunity; and conditions such as the polycystic ovary syndrome (p. 2253.3). Hypothalamic or pituitary causes include reduced production of gonadotrophins due to inadequate nutrition, excessive exercise, or pituitary trauma (see also Hypogonadism, p. 2252.3); or excess prolactin production (see Hyperprolactinaemia, p. 2252.2). Other causes, including adrenal disorders, thyroid disorders, abnormalities of the vagina or uterus, or testicular feminisation, may be found rarely.

The management of amenorrhoea essentially involves the identification of any underlying disorder and its correction, if possible. When the cause cannot be corrected, oestrogen replacement therapy, usually in the form of an oral contraceptive, is appropriate to minimise the consequences of long-term oestrogen deficiency.

References.

1. McIver B, *et al.* Evaluation and management of amenorrhea. *Mayo Clin Proc* 1997; 72: 1161–9.
2. Baird DT. Amenorrhoea. *Lancet* 1997; 350: 275–9.
3. Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril* 2008; 90 (suppl 3): S219–S225.

Cryptorchidism

The testes are formed within the abdomen and subsequently descend the inguinal canal to the scrotum. Failure of the testes to descend (cryptorchidism) occurs in about 3 to 6% of newborn males but in many the testes descend during the first year of life decreasing the prevalence to about 1%. In children with cryptorchidism, pathological testicular damage has been noted by the age of 1 year, and may result in subsequent infertility; cryptorchidism also significantly increases the risk of testicular cancer. Abnormalities of the testes and anatomical abnormalities such as inguinal hernia may contribute to maldescent, and both primary testicular disease and gonadotrophin deficiency may be associated with cryptorchidism. For discussions of Hypogonadism and Infertility, see below and p. 2253.1, respectively. Cryptorchidism should be distinguished from retractile testes in which the testes develop normally and for which treatment is usually not required.

Although cryptorchidism is common, there is no consensus on the best treatment: surgery is commonly used in the USA whereas primary hormonal treatment is more popular in Europe.[1,2]

Surgery is successful in almost all cases, and is usually undertaken at around 1 year of age.[1,2] Primary hormonal therapy generally uses chorionic gonadotrophin or gonadorelin to stimulate androgen production. Success rates vary but reports are difficult to compare because of differences in patient age and treatment regimens, and the possible inclusion of retractile testes. Systematic reviews[3,4] suggest that gonadorelin and chorionic gonadotrophin are more effective than placebo with a success rate of about 20% overall, although this may be considerably lower if care is taken to exclude retractile testes. The lower the position of the undescended testis, the more likely benefit from hormonal therapy appears to be.[3,5] Treatment may also be less successful as boys grow older, and treatment before 12 to 18 months[6] or 2 years of age[4] has been recommended. Some reports suggest that results may be improved by combined therapy with gonadorelin and chorionic gonadotrophin,[7] but others have found no advantage over single drug therapy.[8,9] Surgery is used second-line when hormonal treatment is unsuccessful. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, which may be a predictor of future fertility.[6] Chorionic gonadotrophin may also be useful as an adjuvant before surgery, in order to cause a non-palpable testis to become palpable;[10] however, changes suggestive of inflammation in the testis have been reported after such treatment.[5]

Even after successful treatment, however, there may still be impaired fertility.[1,2,6] Similarly, the risk of testicular cancer is not necessarily reduced to that found in the general population, although there is some evidence that prepubertal surgery may decrease the risk of testicular cancer more than postpubertal treatment.[6] Also, orchidopexy does facilitate testicular examination to enable early detection,[2] and all patients should be monitored.

1. Brucker-Davis F, *et al.* Update on cryptorchidism: endocrine, environmental and therapeutic aspects. *J Endocrinol Invest* 2003; **26**: 575–87.
2. Kolon TF, *et al.* Cryptorchidism: diagnosis, treatment, and long-term prognosis. *Urol Clin North Am* 2004; **31**: 469–80.
3. Pyörälä S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; **80**: 2795–9.
4. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; **20**: 357–9.
5. Kaleva M, *et al.* Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. *Int J Androl* 1996; **19**: 293–8.
6. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (update March 2009). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Paediatric_Urology.pdf (accessed 20/10/09)
7. Giannopoulos MP, *et al.* 13 Year's experience with the combined hormonal therapy of cryptorchidism. *Horm Res* 2001; **55**: 33–7.
8. Bertelloni S, *et al.* Hormonal treatment for unilateral inguinal testis: comparison of four different treatments. *Horm Res* 2001; **55**: 236–9.
9. Esposito C, *et al.* Comparison of five different hormonal treatment protocols for children with cryptorchidism. *Scand J Urol Nephrol* 2003; **37**: 246–9.
10. Polascik TJ, *et al.* Reappraisal of the role of human chorionic gonadotropin in the diagnosis and treatment of the nonpalpable testis: a 10 year-old experience. *J Urol (Baltimore)* 1996; **156**: 804–6.

Delayed puberty

The onset of puberty is associated with an increase in the secretion of luteinising hormone. There is a subsequent increase in concentrations of sex hormones, the development of secondary sexual characteristics, and an associated growth spurt. Delayed puberty is diagnosed when there is no breast development by 13.4 years of age in girls, and no testicular enlargement by 14 in boys. In addition to the various causes of hypogonadism (see below), some of which may be difficult to diagnose, severe systemic illness such as asthma or diabetes, or hypothyroidism, may cause delay in sexual maturation. Where no apparent cause can be found a family history of delayed maturation may suggest constitutional delayed puberty, in which normal pubertal development can eventually be expected.

Where pubertal delay is secondary to some other condition appropriate management of the precipitating cause is required. In constitutional delayed puberty small doses of oestrogens in girls, or androgens (such as oxandrolone or a testosterone ester) in boys, may be given to promote growth and sexual development if psychological problems are apparent. Care is required as overly aggressive therapy with sex hormones may lead to premature closure of the epiphyses and compromise final adult height. Treatment should be interrupted periodically to see if spontaneous pubertal development has begun. Sex hormone replacement is also used in children with hypogonadism, which may be difficult to distinguish from constitutional delay. In boys with hypogonadotrophic hypogonadism, testosterone will induce virilisation but gonadotrophins are needed to stimulate testicular development. Treatment with chorionic gonadotrophin, plus either human menopausal gonadotrophins or follicle-stimulating hormone, provides the required luteinising and follicle-stimulating hormone effects. Alternatively, pulsatile gonadorelin may be given to stimulate endogenous production of these hormones in patients who have hypothalamic dysfunction but are still able to secrete gonadotrophins.

References.
1. De Luca F, *et al.* Management of puberty in constitutional delay of growth and puberty. *J Pediatr Endocrinol Metab* 2001; **14** (suppl): 953–7.
2. Traggiai C, Stanhope R. Delayed puberty. *Best Pract Res Clin Endocrinol Metab* 2002; **16**: 139–51.
3. Pozo J, Argente J. Ascertainment and treatment of delayed puberty. *Horm Res* 2003; **60** (suppl 3): 35–48.
4. Delemarre EM, *et al.* Inducing puberty. *Eur J Endocrinol* 2008; **159** (suppl): S9–S15.

Endometriosis

Gonadorelin analogues are used in the management of endometriosis (see p. 2264.1) but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy, with concomitant hormone replacement, can be used to prevent this.

Hyperprolactinaemia

Hyperprolactinaemia is a condition of elevated circulating prolactin concentrations. It occurs for physiological reasons in pregnancy or after mechanical stimulation of the nipple, as in suckling. However, hyperprolactinaemia may also be an adverse effect of drugs that inhibit dopaminergic function, such as antipsychotics and metoclopramide; other drugs causing hyperprolactinaemia include opioid analgesics, methyldopa, reserpine, oestrogens, SSRIs, and verapamil. Furthermore, pathological hyperprolactinaemia may be associated with prolactin-secreting pituitary adenomas (prolactinomas), damage to the pituitary stalk or hypothalamus (including that caused by non-secreting tumours), or trauma to the chest wall; it may also be associated with disorders such as Cushing's syndrome or hypothyroidism. Prolactinomas are amongst the commonest pathological causes, and so-called idiopathic hyperprolactinaemia, in which no apparent cause is found, may in fact represent undetected microadenoma.

The consequences of hyperprolactinaemia include suppression of ovarian function in women, leading to erratic cycles or amenorrhoea, and infertility (see also p. 2251.3 and p. 2253.1 respectively); in men, in whom the condition is less common, reduced gonadotrophin production leads to testosterone deficiency, diminished libido, and impotence. Both sexes may develop unwanted milk flow (galactorrhoea), although this also requires the presence of oestrogens; men may rarely develop gynaecomastia (p. 2264.3) due to the change in oestrogen/androgen balance.

Management of hyperprolactinaemia depends on its cause. Pathological hyperprolactinaemia must be distinguished from physiological, and where it is secondary to another disease this should be managed appropriately; any drug thought likely to be causative should be withdrawn if possible. Some patients are asymptomatic, or are untroubled by their symptoms; whether such patients should be treated has been a matter of some controversy, although the risk of osteoporosis in women with prolonged suppression of ovarian function has been cited as a reason for such treatment.[1]

In many cases hyperprolactinaemia will be secondary to a prolactinoma. These are generally classified as microadenomas (less than 10 mm in size) or macroadenomas (over 10 mm in size); macroadenomas are often associated with prolactin concentrations more than 10 times the normal upper limit and their rapid expansion may result in visual defects and headache. Initially a course of treatment with a dopamine agonist such as bromocriptine, while rarely curative, is extremely effective in controlling hyperprolactinaemia and restoring gonadal function.[2,3] Surgical removal is now rarely indicated, although transsphenoidal decompression may be necessary for macroadenomas despite bromocriptine therapy, and ultimately radiotherapy may also be required.

The most extensively used dopamine agonist is bromocriptine; it decreases prolactin secretion and reduces tumour size in the majority of patients.[2] There are reports of maintained normoprolactinaemia and reduced tumour size when bromocriptine has been withdrawn after about 2 to 4 years of treatment.[4] However, this occurs in only a minority of patients, and macroadenomas in particular can re-expand, sometimes rapidly, when treatment is stopped.[2] It has been suggested[5] that when the prolactin concentration has been normal for 2 years and the tumour has decreased by at least 50%, the dose of bromocriptine can be gradually reduced, with close follow-up to detect tumour enlargement. The short half-life and the adverse effects of bromocriptine may pose problems, although depot formulations can minimise these. Giving oral prednisolone with intramuscular depot bromocriptine has been reported to reduce the incidence of adverse effects.[5]

Treatment of hyperprolactinaemia restores ovulation in the majority of female patients. In those who become pregnant it is generally advised that fetal exposure to the dopamine agonist should be as short as possible, and therefore stopped when pregnancy is confirmed. Bromocriptine is the drug of choice for patients who are planning pregnancy, because most experience exists with its use compared with other dopamine agonists. The hyperoestrogenic state of pregnancy itself can stimulate prolactinoma growth and patients must be carefully monitored throughout gestation. If symptomatic tumour growth occurs, bromocriptine may be restarted, which is probably less harmful to the mother and fetus than surgery. Surgical debulking before pregnancy has been advocated by some, but may not prevent symptomatic tumour enlargement during pregnancy.[2,6]

Alternative dopaminergic treatments include cabergoline and quinagolide.[2,7] Cabergoline appears to be more effective, and better tolerated, than bromocriptine, and can also be effective in patients who do not respond to bromocriptine. It is considered by some to be a first-line alternative, although bromocriptine is favoured in women who wish to become pregnant. Quinagolide appears to be of similar efficacy to bromocriptine, and may be useful in patients intolerant of or unresponsive to other drugs. Pergolide has also been tried, with similar efficacy to bromocriptine, but it is not licensed for such use.

1. Sanfilippo JS. Implications of not treating hyperprolactinemia. *J Reprod Med* 1999; **44**: 1111–15.
2. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. *Pituitary* 2002; **5**: 55–65.
3. Schlechte JA. Prolactinoma. *N Engl J Med* 2003; **349**: 2035–41.
4. Passos VQ, *et al.* Long-term follow-up of prolactinomas: normoprolactinemia after bromocriptine withdrawal. *J Clin Endocrinol Metab* 2002; **87**: 3578–82.
5. Jenkins PJ, *et al.* Oral prednisolone supplement abolishes the acute adverse effects following initiation of depot bromocriptine therapy. *Clin Endocrinol (Oxf)* 1996; **45**: 447–51.
6. Randeva HS, *et al.* Prolactinoma and pregnancy. *Br J Obstet Gynaecol* 2000; **107**: 1064–8.
7. Bankowski BJ, Zacur HA. Dopamine agonist therapy for hyperprolactinemia. *Clin Obstet Gynecol* 2003; **46**: 349–62.

Hypogonadism

Hypogonadism (decreased or absent gonadal function) may occur in both men and women, and may be either primary, due to some dysfunction of the gonads themselves, or secondary, due to hypopituitarism or some other cause of decreased gonadotrophic stimulation.

Primary ovarian dysfunction may be due to failure of the ovaries to form normally, as in Turner's syndrome (see p. 2254.3), or their degeneration before puberty; there may be premature failure, effectively an early menopause, due to low initial follicle numbers or to destruction of follicles by autoantibodies, chemotherapy, radiotherapy, infection, or trauma. Primary testicular dysfunction may be due to congenital disorders such as Klinefelter's syndrome (associated with an XXY chromosome constitution); the effects of chemotherapy, radiotherapy, infections (particularly mumps), or trauma; and a few other conditions such as testicular degeneration.

Secondary hypogonadism may be due to general hypopituitarism, or to a specific deficiency of gonadotrophin production, or gonadorelin production. Kallmann's syndrome is a congenital disorder of hypogonadotrophic hypogonadism due to gonadorelin deficiency associated with anosmia or hyposmia. The causes of pituitary or hypothalamic failure include neoplasms, radiotherapy to the head and neck, trauma, or infiltrative granulomatous diseases such as tuberculosis. Gonadotrophin production may also be suppressed by various drugs (notably exogenous sex steroids and continuous, rather than pulsatile, use of gonadorelin analogues), by weight loss or inadequate nutrition, by excessive exercise, by severe systemic illness, and by hyperprolactinaemia (see above).

The fundamental treatment for primary hypogonadism is replacement therapy with sex hormones to produce appropriate sexual development and activity and counteract effects such as osteoporosis, but fertility cannot usually be restored. In prepubertal children, the induction of secondary sexual characteristics must be balanced against a possible reduction in final height due to premature closure of the bone epiphyses (see also Delayed Puberty, p. 2252.1). Women are generally given an oestrogen with a progestogen, and men are treated with androgens, often in the form of a long-acting testosterone ester such as the cipionate or enantate given intramuscularly. Transdermal testosterone is also effective.

The cause of secondary hypogonadism should be determined and managed appropriately if possible. In some cases this may be adequate to restore gonadal function but in other cases sex hormone replacement therapy as in primary hypogonadism will be required. Where there is no fundamental defect in gonadal function the possibility of using a gonadotrophic hormone or stimulating the release of gonadotrophins also exists. In general, however, such therapy is often reserved for attempts to restore fertility (see under Infertility, below), since it is inconvenient and expensive.

Further references.

1. Silveira LFG, *et al.* Hypogonadotropic hypogonadism. *Semin Reprod Med* 2002; 20: 327–38.
2. AACE Hypogonadism Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update. *Endocr Pract* 2002; 8: 439–56. Also available at: http://www.aace.com/pub/pdf/guidelines/hypogonadism.pdf (accessed 05/07/06)
3. Lanfranco F, *et al.* Klinefelter's syndrome. *Lancet* 2004; 364: 273–83.
4. Nelson LM. Primary ovarian insufficiency. *N Engl J Med* 2009; 360: 606–14.

Infertility

Although about one couple in 6 may have sufficient difficulty in conceiving children that they seek medical help, most are subfertile rather than infertile, and may eventually conceive, with or without treatment. Several possible treatments are available, but which is used depends upon the cause of the problem. Reduced fertility can have its origins in the male or the female partner or may be due to a combination of factors from both.

The most obvious cause of infertility is a failure of either ovulation in the female or spermatogenesis in the male. Such failures may be due to damage or abnormal formation of the gonads, a failure of hypothalamic/pituitary stimulation, abnormal feedback as in the polycystic ovary syndrome, or suppression of gonadal function as in hyperprolactinaemia. These conditions and their management are briefly discussed under Hypogonadism (p. 2252.3), Polycystic Ovary Syndrome (PCOS; below), and Hyperprolactinaemia (p. 2252.2).

Female factors. The primary problem in about 20% of infertile women is ovulatory dysfunction, and most of these women will have PCOS. *Clomifene* is often used first-line to stimulate ovulation in women with hypothalamic dysfunction, as in PCOS,[1–4] and has been reported to produce ovulation in about 70% of anovulatory women. Alternatively, *metformin* or a combination of clomifene and metformin may be used.[4] Women with PCOS who do not respond to clomifene may be treated with ovarian drilling (laparoscopic diathermy),[2,4] or metformin may be added to clomifene if the combination has not already been tried.[4] The addition of a mid-cycle injection of chorionic gonadotrophin has also been tried for women who fail to ovulate with clomifene,[1] and to define the optimal time for intra-uterine insemination,[2] but such a regimen has not been proven to be better. Some women with clomifene-resistant anovulation may benefit from the sequential use of clomifene and a gonadotrophin that has follicle-stimulating activity.[2] In women with elevated dehydroepiandrosterone concentrations, the addition of a corticosteroid to clomifene may improve the ovulation rate.[1,2] Because of concerns about a possibly increased risk of ovarian cancer, opinion varies as to the maximum number of cycles for which clomifene should be used, but is usually a maximum of 6 cycles (see Carcinogenicity, p. 2259.2). *Tamoxifen* has been used as an alternative in those who cannot tolerate clomifene.[3] Aromatase inhibitors such as *letrozole* have also been tried, and seem to be at least as effective as clomifene in inducing ovulation,[5,6] although concerns about the potential for maternal or fetal toxicity remain to be assuaged.

Gonadotrophins with follicle-stimulating activity can be given directly to women with PCOS who have not ovulated with clomifene.[4] Women with hypothalamic anovulation or hypogonadotrophic hypogonadism generally require gonadotrophins that also have luteinising hormone activity, because of low endogenous levels.[4,7] There is growing interest in the use of recombinant luteinising hormone in these patients.[7] Various regimens have been used but in general, follicle-stimulating hormone is given until a dominant follicle is suitably mature, and then chorionic gonadotrophin is given to trigger ovulation and provide luteal support.[7] The risks of ovarian hyperstimulation syndrome and multiple pregnancies are considerable however, particularly in PCOS, and close monitoring is mandatory using ovarian ultrasound to assess follicle development.[3,4]

Another method used for anovulation is pulsatile *gonadorelin*[4] (gonadotrophin-releasing hormone). It is mainly indicated in women with hypothalamic causes of anovulation; it is less effective in women with PCOS than in hypogonadotrophic patients.

Where anovulation is secondary to hyperprolactinaemia, treatment with dopamine agonists such as bromocriptine can restore fertility (see Hyperprolactinaemia, p. 2252.2).

Where infertility is due to obstruction of the fallopian tubes or intra-uterine adhesions, surgery may be effective for some women.[4] If infection is the cause, appropriate anti-infective agents may be useful. (See also under Pelvic Inflammatory Disease, p. 196.3.)

Endometriosis (p. 2264.1) is another important cause of infertility in women, although the reason for the association is not fully understood. Medical treatment of endometriosis does not enhance fertility, although conservative surgery may do so.[4]

Various other drugs have been used, on a more or less empirical basis. Growth hormone or one of its analogues has been used as an adjunct to ovarian stimulation with gonadotrophins but is not considered to improve pregnancy rates.[4]

Assisted reproduction may be considered when other methods fail. IVF is the most commonly used technique, in which oocytes are retrieved from the ovaries, fertilised *in vitro*, and resulting embryos are selected for transfer to the uterus. Less common techniques include transfer into a fallopian tube of gametes (an unfertilised egg and sperm) or a zygote (fertilised egg). Unlike ovulation induction described above, assisted reproduction techniques intentionally use ovarian hyperstimulation regimens to produce multiple oocytes for retrieval; women are therefore at risk of the ovarian hyperstimulation syndrome and should be monitored appropriately.[4] The most commonly used regimens are the 'long protocols' in which a *gonadorelin agonist* is started in the midluteal phase of the menstrual cycle to desensitise the pituitary and prevent a premature surge of luteinising hormone. When pituitary and ovulation suppression has been achieved, gonadotrophins (human menopausal gonadotrophins or follicle-stimulating hormone) are given to stimulate follicle production. At the appropriate stage of follicular development, a single dose of chorionic gonadotrophin is given to trigger ovulation. These 'long protocols' appear to give better results than short ('flare-up') or ultrashort regimens, in which gonadorelin agonists are given for less time, although short regimens may be useful in poor responders.[7] Guidelines advise that gonadorelin agonists should only be given to women with a low risk of ovarian hyperstimulation syndrome, and that either urinary or recombinant gonadotrophins may be used for ovarian stimulation and triggering ovulation.[4] *Gonadorelin antagonists*, such as cetrorelix and ganirelix, are used as an alternative to gonadorelin agonists. Pituitary desensitisation occurs more rapidly and shorter treatment regimens are used, live birth rates are similar, and the incidence of severe ovarian hyperstimulation syndrome is significantly lower with antagonists.[8] *Progesterone* is the preferred drug for luteal support for IVF procedures because of the increased likelihood of ovarian hyperstimulation syndrome with chorionic gonadotrophin.[4]

Male factors. Impaired male fertility may result from urogenital abnormalities, infections of the genital tract, increased scrotal temperature associated with varicocele, endocrine disturbances, genetic abnormalities, and immunological factors, but 30 to 40% of cases may be idiopathic, where no causal factor is found.[9] Some forms of obstructive azoospermia can be corrected surgically. Varicocele repair with surgery, percutaneous embolisation, or sclerotherapy may be considered in some men but the effects on fertility outcome are unclear.[9–11]

In men with hypogonadotrophic hypogonadism, replacement therapy with a gonadotrophin that has luteinising hormone activity, such as chorionic gonadotrophin or recombinant luteinising hormone, is given to stimulate testosterone production. Menopausal gonadotrophins, or the more specific follicle-stimulating hormone, are then added to stimulate spermatogenesis.[9,10,12] Spermatozoa may appear in the ejaculate after about 6 to 9 months of treatment, but may take considerably longer in some men.[10] Pulsatile gonadorelin may restore gonadotrophin secretion and correct infertility in men with hypogonadotrophic hypogonadism of hypothalamic origin, such as those with Kallmann's syndrome;[9,10,12] therapy for 1 to 2 years may be necessary to achieve adequate sperm production in patients who developed hypogonadism before puberty and have not previously received gonadotrophins or gonadorelin.[9]

In idiopathic oligospermia, results of drug therapy have been disappointing. Corticosteroids have been used in men with autoantibodies to spermatozoa, but efficacy is unproven and corticosteroids are generally not recommended[4,9,10] although they might be considered in men with autoantibodies who have failed assisted reproduction techniques.[10] However, corticosteroids may have a beneficial effect on infertility associated with auto-immune orchitis.[10] Various other drugs have been used on an empirical basis for idiopathic male infertility but evidence for their efficacy is either limited or lacking.[9,10]

When other methods fail, assisted reproduction may be considered. Techniques for male infertility include intra-uterine insemination and intracytoplasmic sperm injection.[4,10,11]

1. ACOG Committee on Practice Bulletins—Gynecology. Management of infertility caused by ovulatory dysfunction. *Obstet Gynecol* 2002; 99: 347–58.
2. Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in women. *Fertil Steril* 2006; 86 (Issue 5 suppl 1): S187–S193.
3. Anonymous. Managing anovulatory infertility. *Drug Ther Bull* 2004; 42: 28–32.
4. NICE. Fertility: assessment and treatment for people with fertility problems (issued February 2013). Available at: http://www.nice.org.uk/nicemedia/live/14078/62769/62769.pdf (accessed 30/10/13)
5. Holzer H, *et al.* A new era in ovulation induction. *Fertil Steril* 2006; 85: 277–84.
6. Eckmann KR, Kockler DR. Aromatase inhibitors for ovulation and pregnancy in polycystic ovary syndrome. *Ann Pharmacother* 2009; 43: 1338–46.
7. Hulme JAF, *et al.* Contemporary pharmacological manipulation in assisted reproduction. *Drugs* 2004; 64: 297–322.
8. Al-Inany HG, *et al.* Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2011 (accessed 07/11/13).
9. Jungwerth A, *et al.* European Association of Urology. Guidelines on male infertility (issued March 2013). Available at: http://www.uroweb.org/gls/pdf/16_Male_Infertility_LRV2.pdf (accessed 07/11/13)
10. Haidl G. Management strategies for male factor infertility. *Drugs* 2002; 62: 1741–53.
11. Jarow JP, *et al.* Best practice policies for male infertility. *J Urol (Baltimore)* 2002; 167: 2138–44.
12. Bhasin S. Approach to the infertile man. *J Clin Endocrinol Metab* 2007; 92: 1995–2004.

Polycystic ovary syndrome

The polycystic ovary syndrome comprises enlargement of the ovaries with multiple follicular cysts and a thickened, whitish, capsule; there is persistent elevation of serum luteinising hormone concentrations, with a tendency to increased androgen concentrations. Women typically present with erratic menstruation, hirsutism, and obesity, although not all these features may be present; fertility is often impaired. Associated metabolic changes include hyperinsulinaemia with insulin resistance, and increased risk of developing hyperlipidaemia, hypertension, and ischaemic heart disease. The risk of endometrial cancer is also increased.

Management is essentially symptomatic. Patients should be encouraged to modify their lifestyle, to correct lipid abnormalities, and to lose weight if obese;[1,2] weight loss alone may be sufficient to improve menstrual regularity, hirsutism, and fertility. Symptoms of hyperandrogenism can be treated with an anti-androgen, such as cyproterone acetate or spironolactone, with an oestrogen or a combined contraceptive pill.[1–5] Flutamide and finasteride have also been used in these patients (see also the discussion of the management of hirsutism, p. 2262.1).[5] In women who do not desire pregnancy, an oral contraceptive is also the recommended treatment for amenorrhoea or oligomenorrhoea.[2,5–7] Alternatively a progestogen that lacks androgenic properties may be given cyclically, in order to induce withdrawal bleeding (anovular women who do not receive hormonal treatment may be at increased risk of endometrial cancer).[3,6,7] Metformin may also improve metabolic abnormalities and menstrual regularity (see also below), and endocrinologists in the USA have suggested that it may be considered particularly for women who are overweight or obese.[1] Long-term effects of metformin in polycystic ovary syndrome have not been studied, however, and any reduction in cardiovascular risks is yet to be established.[8] Other practitioners have argued that weight reduction is more effective and should be the initial management for obese women with polycystic ovary syndrome.[2]

In patients who wish to conceive, clomifene citrate is used to induce ovulation. In patients who do not respond, gonadotrophins or laparoscopic ovarian diathermy may be tried. When these have not been successful, IVF may be considered. The effects of metformin on ovulation induction are also under investigation (see below).[2,3,6,7,9] Patients must be monitored carefully during any therapy to induce ovulation, as women with polycystic ovaries are more prone to multiple follicle development and ovarian hyperstimulation. For further details on ovulation induction and assisted reproduction, see Infertility, above.

Insulin resistance is a feature of polycystic ovary syndrome, particularly in obese women. Small non-randomised studies of metformin have reported

improvements in insulin metabolism, a reduction in circulating androgen concentrations, small reductions in body-mass index or waist/hip ratio, and improvements in *menstrual cycles*.[10,11] *Early controlled studies found that* metformin alone improved ovulation rates and menstrual cycles, and that rates could be improved further when it was given with clomifene citrate.[10] However, 2 large, placebo-controlled studies later found that metformin, either alone or with clomifene, did not improve the rate of ovulation, pregnancy, or live births in women with polycystic ovary syndrome.[2] A subsequent meta-analysis[12] concluded that although there was some evidence for improvements in pregnancy and ovulation rates with metformin, this did not lead to increases in live birth rates (whether it was used alone or with clomifene). Another meta-analysis[13] concluded that metformin did not improve live birth rates in clomifene therapy-naive women, but there was evidence of better rates when metformin was added to clomifene therapy in clomifene-resistant women. Based on limited data, it also appeared that there was no benefit from the addition of metformin to laparoscopic ovarian drilling or follicle-stimulating hormone. Consensus opinion is that metformin should not be used first-line for management of infertility in PCOS, and should be restricted to women with glucose intolerance.[9] There has also been some interest in the use of thiazolidinediones, such as rosiglitazone, but these drugs can increase body-mass, which is undesirable in women who are already overweight.[5,10,11] Their use is considered investigational.[1]

Bromocriptine[4] may be useful in women with polycystic ovary syndrome and associated hyperprolactinaemia (see p. 2252.2).

1. AACE Polycystic Ovary Syndrome Writing Committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. *Endocr Pract* 2005; 11: 126–34. Also available at: http://www.aace.com/pub/pdf/guidelines/PCOSpositionstatement.pdf (accessed 21/10/09)
2. Norman RJ, *et al.* Polycystic ovary syndrome. *Lancet* 2007; 370: 685–97.
3. Anonymous. Tackling polycystic ovary syndrome. *Drug Ther Bull* 2001; 39: 1–5.
4. Hyperandrogenic Disorders Task Force. American Association of Clinical Endocrinologists medical guidelines for the clinical practice for the diagnosis and treatment of hyperandrogenic disorders. *Endocr Pract* 2001; 7: 121–34. Also available at: http://www.aace.com/pub/pdf/guidelines/hyperandrogenism2001.pdf (accessed 05/07/06)
5. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med* 2005; 352: 1223–36.
6. ACOG Committee on Practice Bulletins—Gynecology. Polycystic ovary syndrome. *Obstet Gynecol* 2002; 100: 1389–1402.
7. Guzick DS. Polycystic ovary syndrome. *Obstet Gynecol* 2004; 103: 181–93. Correction. *ibid.*; 799.
8. Royal College of Obstetricians and Gynaecologists. Long-term consequences of polycystic ovary syndrome (Guideline no. 33 issued December 2007). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT33_LongTermPCOS.pdf (accessed 20/07/10)
9. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod* 2008; 23: 462–77. Also published in *Fertil Steril* 2008; 89: 505–22.
10. Harborne L, *et al.* Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. *Lancet* 2003; 361: 1894–1901.
11. Katsiki N, *et al.* The role of insulin-sensitizing agents in the treatment of polycystic ovary syndrome. *Drugs* 2009; 69: 1417–31.
12. Tang T, *et al.* Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 20/07/10).
13. Moll E, *et al.* The role of metformin in polycystic ovary syndrome: a systematic review. *Hum Reprod Update* 2007; 13: 527–37.

Precocious puberty

Precocious puberty is commonly understood to mean the development of secondary sexual characteristics before the age of 8 years in girls or 9 years in boys; it is four to five times more common in girls. However, the age limit used to define precocious puberty in girls has been questioned.[1] Recent data from the United States suggest that puberty is occurring earlier in girls, at age 7 years for white girls, and 6 years for African-American girls. Precocious puberty is either central, due to premature activation of the hypothalamic-pituitary-gonadal axis, or peripheral, due to secretion of extrapituitary gonadotrophins or gonadal steroids independent of gonadorelin secretion from the hypothalamus or pituitary gonadotrophins. In many cases the cause is not apparent, and they are classified as idiopathic. A small proportion of cases are due to tumours. Central precocious puberty may be caused by CNS lesions secondary to diseases such as encephalitis, meningitis, or granuloma, or due to head trauma. Peripheral precocious puberty can be associated with congenital or familial syndromes such as McCune-Albright syndrome or familial testotoxicosis (familial male precocious puberty). Congenital adrenal hyperplasia (see p. 1603.2) can also produce premature sexual development in boys and virilisation in girls.

Apart from early sexual maturation and the associated emotional distress, the chief clinical consequence of precocious puberty is short stature as an adult, due to premature closure of the epiphyses under the influence of sex steroids.[2,3] Age, emotional impact and final height potential should be considered in deciding when to begin and end treatment.[2]

Gonadorelin analogues are the treatment of choice in central precocious puberty.[2,3] The use of continuous rather than pulsatile gonadorelin can paradoxically suppress gonadotrophin secretion by desensitisation and down regulation of pituitary receptors. Cyproterone acetate has been given at the beginning of treatment to prevent the initial stimulatory effect of the gonadorelin analogue.[2] *Although originally given daily, by subcutaneous injection* or nasal insufflation, intramuscular and subcutaneous depot preparations of gonadorelin analogues are more convenient, and are now more widely used.[2,3] Treatment suppresses sexual development and skeletal maturation, and most studies have reported an improvement in final height.[3,4] However, *the treatment of girls with borderline early* puberty (between 6 and 8 years of age) has been questioned, as studies suggest that most will reach adult height within the normal range without treatment.[1] Such girls with idiopathic slowly progressing puberty, and no evidence of advanced bone age, may not require gonadorelin therapy, but should be monitored for an onset of rapid pubertal development.[1,5] Children with concomitant growth hormone deficiency (for example after cranial irradiation) may need additional therapy with somatropin or its analogues for maximum benefit.[6] Somatropin has also been used in children who do not have growth hormone deficiency but who have a poor response to gonadorelin analogue therapy; evidence for a beneficial effect is limited.[7]

In the peripheral forms of precocious puberty the gonadorelin analogues are ineffective. Any underlying condition such as a gonadal or adrenal neoplasm should be sought and treated appropriately. Otherwise, therapy is aimed at suppressing premature sexual maturation, and drugs such as cyproterone and medroxyprogesterone have been used.[8] In girls with precocious puberty associated with the McCune-Albright syndrome, the aromatase inhibitor testolactone has been used with some success to block oestrogen biosynthesis,[9,10] ketoconazole has been used in 2 cases,[11] and tamoxifen has been reported to be beneficial.[12] Although ineffective when given alone, testolactone was reported to be of benefit when used with the anti-androgen, spironolactone, in boys with testotoxicosis;[13] a reduction in the rate of bone maturation was reported. Response diminished with long-term treatment, but could be restored by the addition of a gonadorelin analogue, deslorelin, to therapy.[14] This regimen has also been reported[15] to improve predicted adult height. Ketoconazole, which has anti-androgenic properties, has also been tried in boys with familial male precocious puberty; it had beneficial effects on testosterone concentrations and adult height reported in a series of 5 patients.[16]

1. Kaplowitz PB, *et al.* Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. *Pediatrics* 1999; 104: 936–41.
2. Merke DP, Cutler GB. Evaluation and management of precocious puberty. *Arch Dis Child* 1996; 73: 269–71.
3. Partsch C-J, *et al.* Management and outcome of central precocious puberty. *Clin Endocrinol (Oxf)* 2002; 56: 129–48.
4. Klein KO, *et al.* Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; 86: 4711–16.
5. Léger J, *et al.* Do all girls with apparent idiopathic precocious puberty require gonadotropin-releasing hormone agonist treatment? *J Pediatr* 2000; 137: 819–25.
6. Adan L, *et al.* Adult height in 24 patients treated for growth hormone deficiency and early puberty. *J Clin Endocrinol Metab* 1997; 82: 229–33.
7. Walvoord EC, Pescovitz OH. Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: theoretic and practical considerations. *Pediatrics* 1999; 104 (suppl): 1010–14.
8. Stanhope R, Traggiai C. Precocious puberty (complete, partial). *Endocr Dev* 2004; 7: 57–65.
9. Peuillan PP, *et al.* Long term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab* 1993; 77: 647–51.
10. Albers N, *et al.* McCune-Albright syndrome - the German experience. *J Pediatr Endocrinol Metab* 2002; 15 (suppl): 897–901.
11. Syed FA, Chalew SA. Ketoconazole treatment of gonadotropin independent precocious puberty in girls with McCune-Albright syndrome: a preliminary report. *J Pediatr Endocrinol Metab* 1999; 12: 81–3.
12. Eugster EA, *et al.* Tamoxifen treatment for precocious puberty in McCune-Albright syndrome: a multicenter trial. *J Pediatr* 2003; 143: 60–6.
13. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; 320: 496–502.
14. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; 76: 151–5.
15. 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.
16. Soriano-Guillén L, *et al.* Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. *J Clin Endocrinol Metab* 2005; 90: 147–51.

Premenstrual syndrome

Gonadorelin analogues have been used to treat patients with severe symptoms attributable to the premenstrual syndrome (p. 2272.3), with 'add-back' therapy with oestrogen plus progestogen to prevent the symptoms of oestrogen deficiency.

Turner's syndrome

Turner's syndrome is a congenital disorder associated with the absence of an X or Y chromosome, resulting in an individual with only a single X chromosome who is female in phenotype but in whom the ovaries do not develop. In addition to this gonadal dysgenesis, which results in infertility and primary amenorrhoea, various physical abnormalities may be present including short stature, a short webbed neck and characteristic facial appearance, shield-like chest, multiple naevi, eye and ear disorders, and certain renal and cardiovascular abnormalities. Hypothyroidism and glucose intolerance may occur.

As with other forms of ovarian failure, hormonal therapy is indicated in patients with Turner's syndrome in order to produce sexual maturation and the development of secondary sexual characteristics, as well as to avoid complications such as osteoporosis. Low-dose oestrogen therapy may be started if spontaneous puberty has not begun by 12 to 13 years of age and the follicle-stimulating hormone value is elevated. The dose is gradually increased over 2 to 4 years to promote a normal pace of pubertal development, and a cyclic progestogen is usually added about 2 years after starting oestrogen therapy or when breakthrough bleeding occurs. There is no consensus on which oestrogen is preferred for these patients. Conjugated oestrogens, ethinylestradiol, and estradiol have all been used, but transdermal or injectable depot estradiol may be the most physiological options. An oral contraceptive may be used in adults for maintenance therapy. The duration of oestrogen therapy should be individualised, and adjusted or stopped at the age of normal menopause based on the same considerations used for other postmenopausal women.[1]

A minority of patients with Turner's syndrome have some residual ovarian function, and there are reports of pregnancy in such patients. In women without ovaries it may be possible to maintain pregnancy by appropriate hormone replacement and implantation of a fertilised donor egg.[1]

Short stature is the most common clinical manifestation of Turner's syndrome and growth hormone therapy has been widely used. Results from 622 girls enrolled in the National Cooperative Growth Study[2] suggested a mean height gain of 6.4 ± 4.9 cm, and another cohort database[3] of 485 girls found that when treatment was started before puberty a mean increase in final height of 5 cm or more would be expected. A systematic review[4] of 4 controlled studies found that growth hormone increased short-term growth, and the one study that reported final height found that treated patients were 7 cm taller than untreated ones. Nevertheless, final height in treated patients was about 148 cm, which is still below the normal range for adult women. Growth hormone therapy during childhood and adolescence may also be important in maximising bone mass and reducing the risk of osteoporosis.[5] The optimal age for starting growth hormone therapy has not been established, although studies have found beneficial effects in children as young as 9 months of age. In general, therapy should be considered as soon as growth failure is detected. For girls below about 9 years of age, treatment usually starts with growth hormone alone. For older girls, or those with extremely short stature, higher doses of growth hormone with a non-aromatisable anabolic steroid (such as oxandrolone) may be considered.[1]

There has been some concern that oestrogen therapy might interfere with the effects of growth hormone therapy, and that the timing of pubertal induction would be important in maximising final height. Studies have found that patients who receive growth hormone for a longer period before starting oestrogen therapy attain greater adult height,[6,7] and it has been suggested that optimal height can be achieved by the early use of growth hormone and induction of puberty at an appropriate physiological age.[8] Guidelines now consider that oestrogens can be started at 12 years of age to achieve age-appropriate pubertal maturation without interfering with the positive effects of growth hormone treatment, which should be considered as soon as growth failure is found.[1] However, the use of low-dose oestrogen from an even earlier age (as young as 8 years) to stimulate linear growth does not add to the effect of growth hormone therapy and may even reduce final height.[9]

Patients with Turner's syndrome require multidisciplinary management throughout life, including cardiovascular monitoring, psychological support, and a programme of prevention for diabetes, dyslipidaemia, osteoporosis, and hypertension.[1]

1. Bondy CA. The Turner Syndrome Consensus Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007; 92: 10–25.
2. Plotnick L, *et al.* Growth hormone treatment of girls with Turner syndrome: the National Cooperative Growth Study experience. *Pediatrics* 1998; 102: 479–81.

3. Betts PR, *et al.* A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Arch Dis Child* 1999; 80: 221–5.
4. Baxter L, *et al.* Recombinant growth hormone for children and adolescents with Turner syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 30/12/08).
5. Rubin K. Turner syndrome and osteoporosis: mechanisms and prognosis. *Pediatrics* 1998; 102 (suppl): 481–5.
6. Chernausek SD, *et al.* Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. *J Clin Endocrinol Metab* 2000; 85: 2439–45.
7. Reiter EO, *et al.* Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 2001; 86: 1936–41.
8. Soriano-Guillen L, *et al.* Adult height and pubertal growth in Turner syndrome after treatment with recombinant growth hormone. *J Clin Endocrinol Metab* 2005; 90: 5197–5204.
9. Quigley CA, *et al.* Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. *J Clin Endocrinol Metab* 2002; 87: 2033–41.

Abarelix *(USAN, rINN)*

Abarelix; Abarelixum; PPI-149; R-3827; Абареликс.
N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-*N*-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-*N*-isopropyl-L-lysyl-L-prolyl-D-alaninamide.
$C_{71}H_{95}ClN_{14}O_{14}$=1416.1
CAS — 183552-38-7.
ATC — L02BX01.
ATC Vet — QL02BX01.
UNII — W486S5824.

Uses and Administration

Like cetrorelix (p. 2257.2), abarelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is used to reduce testosterone concentrations in the palliative hormonal therapy of prostate cancer (p. 712.3). A dose of abarelix 100 mg is given intramuscularly on days 1, 15, and 29, and then every 4 weeks thereafter.

Abarelix has been investigated for the treatment of endometriosis.

Malignant neoplasms. References.

1. Tomera K, *et al.* The gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone releasing hormone agonists leuprolide or goserelin: initial results of endocrinological and biochemical efficacies in patients with prostate cancer. *J Urol (Baltimore)* 2001; 165: 1585–9.
2. McLeod D, *et al.* A phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer. *Urology* 2001; 58: 756–61.
3. Trachtenberg J, *et al.* A phase 3, multicenter, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. *J Urol (Baltimore)* 2002; 167: 1670–4.
4. Koch M, *et al.* An open-label study of abarelix in men with symptomatic prostate cancer at risk of treatment with LHRH agonists. *Urology* 2003; 62: 877–82.
5. Kirby RS, *et al.* Abarelix and other gonadotrophin-releasing hormone antagonists in prostate cancer. *BJU Int* 2009; 104: 1580–4.

Adverse Effects and Precautions

Immediate hypersensitivity reactions, including urticaria, pruritus, hypotension, and syncope, can occur with abarelix, and the cumulative risk of such a reaction increases with repeated doses. Patients should be monitored for at least 30 minutes after each injection. Hot flushes, sleep disturbance, breast enlargement and tenderness may result from testosterone reduction. Prolongation of the QT interval has occurred in patients receiving abarelix.

Elevations in transaminase concentrations have occurred, and liver function should be monitored before starting treatment, and periodically during treatment. The efficacy of abarelix in the management of prostate cancer decreases with duration of therapy, and may be further reduced in patients weighing more than about 100 kg (225 pounds). Serum-testosterone should therefore be measured on day 29 of therapy and then every 8 weeks, to monitor for treatment failure.

Pharmacokinetics

Abarelix is absorbed slowly after intramuscular injection; peak serum concentrations occur after about 3 days. It is metabolised by hydrolysis and has an elimination half-life of about 13 days with intramuscular use.

References.

1. Wong SL, *et al.* Pharmacokinetics and pharmacodynamics of a novel depot formulation of abarelix, a gonadotropin-releasing hormone (GnRH) antagonist, in healthy men ages 50 to 75. *J Clin Pharmacol* 2004; 44: 495–502.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Plenaxis; *Ger.*: Plenaxis; *Neth.*: Plenaxis.

Alfatradiol *(rINN)*

Alfatradiolum; Alpha-estradiol; Epiestradiol; 17α-Estradiol; NSC-20293; Альфатрадиол.
Estra-1,3,5(10)-triene-3,17α-diol.
$C_{18}H_{24}O_2$=272.4
CAS — 57-91-0.
UNII — 1VO38D63M7.

Profile

Alfatradiol is the 17-α isomer of estradiol (p. 2271.1) but has much weaker oestrogenic actions. It is a 5α-reductase inhibitor and is used topically as a 0.025% solution for alopecia androgenetica (p. 1682.3).

References.

1. Blume-Peytavi U, *et al.* Comparison of the efficacy and safety of topical minoxidil and topical alfatradiol in the treatment of androgenetic alopecia in women. *J Dtsch Dermatol Ges* 2007; 5: 391–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Avixis; *Ger.*: Ell-Cranell alpha; Pantostin; *Mex.*: Avixis.

Algestone Acetophenide *(USAN, rINNM)*

Acetofenido de alfasona; Acetofenido de algestona; Acetofenido de dihidroxiprogesterona; Algestona, acetofenido de; Algestone; Acetophenide d'; Algestoni Acetophenidum; Alphasone Acetophenide; Dihydroxyprogesterone Acetophenide; SQ-15101; Альгестона Ацетофенид.
16α,17α-(1-Phenylethylidenedioxy)pregn-4-ene-3,20-dione; 16α,17α-Isopropylidenedioxypregn-4-ene-3,20-dione.
$C_{29}H_{36}O_4$=448.6
CAS — 595-77-7 (algestone); 24356-94-3 (algestone acetophenide).
UNII — QL7KC2O3OT.

Profile

Algestone acetophenide is a progestogen (see Progesterone, p. 2300.2) that is given by intramuscular injection in monthly doses of 150 mg, with estradiol enantate, as a hormonal contraceptive (see p. 2231.3). It has also been applied topically in the treatment of acne.

References.

1. Martínez GE, *et al.* Vaginal bleeding patterns in users of Perlutal, a once-a-month injectable contraceptive consisting of 10 mg estradiol enanthate combined with 150 mg dihydroxyprogesterone acetophenide: a trial of 5462 woman-months. *Contraception* 1998; 58: 21–7.
2. Coutinho EM, *et al.* Efficacy, acceptability, and clinical effects of a low-dose injectable contraceptive combination of dihydroxyprogesterone acetophenide and estradiol enanthate. *Contraception* 2000; 61: 277–80.
3. Coutinho EM, *et al.* Comparison of two regimens of a monthly injectable contraceptive containing dihydroxyprogesterone acetophenide and estradiol enanthate. *Contraception* 2006; 73: 249–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Atrimon; Patector; Perlutal; *Braz.*: Daiva; Perlutan; Preg-Less; Pregnolan; Uno Ciclo; *Chile*: Unalmes; *Mex.*: Anafertin; Patector; Perludil; Perlutal; Yectames; *Singapore*: Unijab.

Allylestrenol *(BAN, rINN)*

Alilestrenol; Allylestrénol; Allylestrenolum; Allyloestrenol; Allylöstrenol; Allyyliestrenoli; Аллилэстренол.
17α-Allylestr-4-en-17β-ol.
$C_{21}H_{32}O$=300.5
CAS — 432-60-0.
ATC — G03DC01.
ATC Vet — QG03DC01.
UNII — I47VB5DZ8Q.

Profile

Allylestrenol is a progestogen (see Progesterone, p. 2300.2) structurally related to progesterone that has been given in threatened and recurrent miscarriage, and to prevent premature labour. However, with the exception of proven progesterone deficiency, such use is no longer recommended. In threatened miscarriage in progesterone-deficient women a suggested oral dose is 5 mg three times daily for 5 to 7 days.

Pregnancy. A case-control study of allylestrenol use in pregnancy during 1980 to 1984 in Hungary indicated that it was not teratogenic.[1]

1. Czeizel A, Huiskes N. A case-control study to evaluate the risk of congenital anomalies as a result of allylestrenol therapy during pregnancy. *Clin Ther* 1988; 10: 725–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Gestanon; *Hong Kong*: Turinal†; *India*: Alese; Allynol; Allytry; Anin; Fetugard; Foegard; Fulterm; Gestin; Gravida; Gravidin; Gravinol; Gravion; Gynerol; Gynonys; Iugr; Loestrol; Maintane; Nidagest; Profar; *Indon.*: Alynol; Gravynon; Lestron; Preabor; Pregnolin; Pregtenol; Premaston; Prenolin†; Prestrenol; Progeston; *Malaysia*: Gestrenol; *Philipp.*: Turinal; *Rus.*: Turinal (Туринал)†; *Singapore*: Gestrenol; *Ukr.*: Turinal (Туринал)†.

Altrenogest *(BAN, USAN, rINN)*

A-35957; A-41300; Altrenogest; Altrenogestum; RH-2267; RU-2267; Альтреногест.
17α-Allyl-17β-hydroxy-19-norandrosta-4,9,11-trien-3-one; 17β-Hydroxy-19-21,24-trinorchola-4,9,11,22-tetraen-3-one.
$C_{21}H_{26}O_2$=310.4
CAS — 850-52-2.
ATC Vet — QG03DX90.
UNII — 2U0X01A2NB.

Profile

Altrenogest is a progestogen (see Progesterone, p. 2300.2) used in veterinary medicine.

Androstanolone *(BAN, rINN)* ⊗

Androstanolo; Androstanolon; Androstanolona; Androstanolonum; Dihidrotestosterona; Dihydrotestosterone; Estanolona; Stanolon; Stanolone; Андростанолон.
17β-Hydroxy-5α-androstan-3-one.
$C_{19}H_{30}O_2$=290.4
CAS — 521-18-6.
ATC — A14AA01; G03BB02.
ATC Vet — QA14AA01; QG03BB02.
UNII — 08J2K08A3Y.

Profile

Androstanolone is formed naturally in the body from testosterone (p. 2305.1) by the action of 5α-reductase, and is more active than the parent compound. It has anabolic and androgenic properties and is applied topically in the form of a 2.5% gel for male hypogonadism and gynaecomastia, and for lichen sclerosus in both men and women.

References.

1. Wang C, Swerdloff RS. Should the nonaromatizable androgen dihydrotestosterone be considered as an alternative to testosterone in the treatment of the andropause? *J Clin Endocrinol Metab* 2002; 87: 1462–6.
2. Kunelius P, *et al.* The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab* 2002; 87: 1467–72.
3. Sakhri S, Gooren LJ. Safety aspects of androgen treatment with 5α-dihydrotestosterone. *Andrologia* 2007; 39: 216–22.
4. Kaya C, *et al.* The efficacy of dihydrotestosterone transdermal gel before primary hypospadias surgery: a prospective, controlled, randomized study. *J Urol (Baltimore)* 2008; 179: 684–8.

Lichen sclerosus. For references to the use of androgens such as androstanolone in lichen sclerosus, see under Testosterone, p. 2307.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Andractim; *Fr.*: Andractim; *Singapore*: Andractim.

Androstenedione ⊗

Androstenodiona; Андростендион.
Androst-4-ene-3,17-dione.
$C_{19}H_{26}O_2$=286.4
CAS — 63-05-8.
UNII — 4092J96VR.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of androstenedione:

Andro.

Profile

Androstenedione is a naturally occurring adrenal androgen that is a precursor of androgens and oestrogens (see p. 2231.1). It has been used in an attempt to enhance athletic performance and as hormone replacement for men. In March 2004 the FDA banned the distribution of dietary supplements containing androstenedione, considering them to be adulterated and warning that they did not meet safety requirements.

Action. The effects of androstenedione have been studied in groups of young (under 40 years of age) and older (up to 65 years) men with normal serum testosterone concentrations.[1-4] Testosterone concentrations were reported to remain unchanged[1,4] as well as increase,[2,3] although they returned to baseline in the longer study of 12 weeks.[3] In 3 of the studies, oestrogens (oestradiol and oestrone) increased.[1-3] Changes in lipid profiles were also noted, particularly a decrease in high-density lipoprotein (HDL) cholesterol.[1,3] Androstenedione did not enhance the effects of resistance training.[1,3]

There has been a report of impotence and severe oligospermia associated with ingestion of androstenedione by a bodybuilder.[5] Priapism has also been reported.[6]

1. King DS, *et al.* Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial. *JAMA* 1999; **281:** 2020–8.
2. Leder BZ, *et al.* Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA* 2000; **283:** 779–82.
3. Broeder CE, *et al.* The Andro Project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. *Arch Intern Med* 2000; **160:** 3093–3104.
4. Beckham SG, Earnest CP. Four weeks of androstenedione supplementation diminishes the treatment response in middle aged men. *Br J Sports Med* 2003; **37:** 212–8.
5. Ritter RH, *et al.* Oral androstenedione-induced impotence and severe oligospermia. *Fertil Steril* 2005; **84:** 217.e7–e8.
6. Kachhi PN, Henderson SO. Priapism after androstenedione intake for athletic performance enhancement. *Ann Emerg Med* 2000; **35:** 391–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Thai.*: Metharmon-F†.

Bazedoxifene Acetate *(USAN, rINNM)* ⊗

Acetato de bazedoxifeno; Bazédoxifène, Acétate de; Bazedoxifeni Acetas; TSE-424; WAY-140424; WAY-TSE-424; Базедоксифена Ацетат.

1-[*p*-[2-(Hexahydro-1*H*-azepin-1-yl)ethoxy]benzyl]-2-(*p*-hydroxyphenyl)-3-methylindol-5-ol monoacetate.

$C_{30}H_{34}N_2O_3.C_2H_4O_2$=530.7

CAS — 198481-32-2 (bazedoxifene); 198481-33-3 (bazedoxifene acetate).

ATC — G03XC02.

ATC Vet — QG03XC02.

UNII — J70472UD3D.

Uses and Administration

Bazedoxifene acetate is a selective oestrogen receptor modulator that has oestrogen-receptor agonist effects on bone, and antagonist effects on uterine and breast tissue. It is used in the prevention and treatment of postmenopausal osteoporosis (p. 1168.1) in women at increased risk of fracture. It is also given to reduce the risk of endometrial hyperplasia associated with oestrogen therapy; a combination of conjugated oestrogens with bazedoxifene may be used in the management of moderate to severe menopausal vasomotor symptoms (p. 2245.1), and in the prevention of postmenopausal osteoporosis. Bazedoxifene is given as the acetate, but doses are expressed in terms of the base: 11.3 mg of bazedoxifene acetate is equivalent to about 10 mg of bazedoxifene. For the above indications, an oral dose equivalent to bazedoxifene 20 mg is given once daily.

References.

1. Stovall DW, *et al.* Tissue-selective estrogen complex bazedoxifene and conjugated estrogens for the treatment of menopausal vasomotor symptoms. *Drugs* 2011; **71:** 1649–57.
2. Duggan ST, McKeage K. Bazedoxifene: a review of its use in the treatment of postmenopausal osteoporosis. *Drugs* 2011; **71:** 2193–2212.
3. Taylor HS, Ohleth K. Using bazedoxifene plus conjugated estrogens for treating postmenopausal women: a comprehensive review. *Menopause* 2012; **19:** 479–85.
4. Pinkerton JV, *et al.* Bazedoxifene/conjugated estrogens for menopausal symptom treatment and osteoporosis prevention. *Climacteric* 2012; **15:** 411–18.
5. Mirkin S, Pickar JH. Management of osteoporosis and menopausal symptoms: focus on bazedoxifene/conjugated estrogen combination. *Int J Womens Health* 2013; **5:** 465–75.

Adverse Effects and Precautions

As for Raloxifene Hydrochloride, p. 2303.3 and p. 2304.1. Other effects reported for bazedoxifene include somnolence and dry mouth. Increases in blood triglycerides and liver enzymes values may also occur commonly.

Pharmacokinetics

Bazedoxifene is absorbed from the gastrointestinal tract, with peak plasma concentrations occurring after about 2 hours. It has an absolute bioavailability of about 6% and is highly bound to plasma proteins. Bazedoxifene is extensively metabolised, mainly by glucuronidation, and eliminated in the faeces via biliary excretion with a half-life of about 30 hours. It is expected to undergo enterohepatic recycling.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Conbriza; *Gr.*: Conbriza; *Irl.*: Conbriza; *Jpn*: Viviant; *Neth.*: Conbriza; *Pol.*: Conbriza; *Port.*: Conbriza; *Spain*: Conbriza; *Switz.*: Conbriza.

Multi-ingredient Preparations. *USA*: Duavee.

Boldenone Undecenoate *(BANM, rINNM)* ⊗

Ba-29038; Boldenone Undecylenate (USAN); Boldénone, Undécylénate de; Boldenoni Undecylenas; 1-Dehydrotestosterone (boldenone); Undecilenato de boldenona; Болденона Ундециленат.

17β-Hydroxyandrosta-1,4-dien-3-one 17-(undec-10-enoate).

$C_{30}H_{44}O_3$=452.7

CAS — 846-48-0 (boldenone); 13103-34-9 (boldenone undecenoate).

UNII — ZS6D2ITA30.

Profile

Boldenone undecenoate is an anabolic steroid (see Testosterone, p. 2305.1) that has been used in veterinary practice. It has been subject to abuse in sport.

Buserelin *(BAN, rINN)* ⊗

Buserelíini; Buserelina; Buserelinas; Busséréline; Buserelinum; Buszerelin; S74-6766; Бусерелин.

(6-*O*-*tert*-Butyl-D-serine)-des-10-glycinamidegonadorelin ethylamide; 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-*tert*-butyl-D-seryl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

$C_{60}H_{86}N_{16}O_{13}$=1239.4

CAS — 57982-77-1.

ATC — L02AE01.

ATC Vet — QH01CA90; QL02AE01.

UNII — PXW8U3YXDV.

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

Ph. Eur. 8: (Buserelin). A white or slightly yellowish hygroscopic powder. Sparingly soluble in water and in dilute acids. Store at 2 degrees to 8 degrees. Protect from light and moisture.

Buserelin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de buserelina; Buserelin Asetat; Buserelina, acetato de; Busséréline, Acétate de; Buserelini Acetas; Hoe-766; D-Ser (Bu^t)^6 Pro^9 NEt LHRH acetate; Бусерелина Ацетат.

$C_{60}H_{86}N_{16}O_{13}.C_2H_4O_2$=1299.5

CAS — 68630-75-1.

ATC — L02AE01.

ATC Vet — QL02AE01.

UNII — 13U86G7YSP.

Uses and Administration

Buserelin is an analogue of gonadorelin (p. 2280.3) with similar properties. It is used for the suppression of testosterone in the treatment of malignant neoplasms of the prostate; it is also used in the treatment of endometriosis and as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility. It has been used in central precocious puberty and tried in the treatment of uterine fibroids (see p. 2257.1 and below respectively). Buserelin is usually given as the acetate but doses are expressed in terms of the base; 105 micrograms of buserelin acetate is equivalent to about 100 micrograms of buserelin.

In advanced **prostatic carcinoma** doses of 500 micrograms are injected subcutaneously every 8 hours for 7 days. On the eighth day treatment is changed to the nasal route; 100 micrograms is sprayed into each nostril 6 times daily (usually before and after meals). An acceptable response should be achieved within 4 to 6 weeks. Since there is an initial increase in circulating testosterone, an anti-androgen such as cyproterone acetate may be given for at least 3 days before beginning buserelin therapy, and continued for at least 3 weeks, to avoid the risk of a disease flare. Long-acting subcutaneous depot preparations that release buserelin over a 2- or 3-month period are also available.

In **endometriosis** a dose of 150 micrograms is sprayed into each nostril three times daily. The usual duration of a course of therapy is 6 months, which should not be exceeded.

In **infertility**, pituitary desensitisation before ovulation induction with gonadotrophins is achieved by giving 150 micrograms intranasally four times daily, beginning either in the early follicular phase (day 1) or midluteal phase (day 21) of the menstrual cycle. Alternatively, 200 to 500 micrograms may be given daily as a subcutaneous injection. Therapy should be continued until pituitary downregulation occurs, which normally takes 1 to 3 weeks; if necessary 300 micrograms four times daily intranasally, or 500 micrograms twice daily subcutaneously may be given. Gonadotrophin treatment is then added to buserelin therapy until an appropriate stage of follicular development, when both are withdrawn and chorionic gonadotrophin is given to induce ovulation.

General reviews.

1. Brogden RN, *et al.* Buserelin: a review of its pharmacodynamic and pharmacokinetic properties, and clinical profile. *Drugs* 1990; **39:** 399–437.

Administration in children. Buserelin may be used in the management of central precocious puberty—see p. 2257.1.

Endometriosis. Gonadorelin analogues such as buserelin have a role in the management of endometriosis (p. 2264.1), but the need for long-term therapy limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References.

1. Lemay A, *et al.* Efficacy of intranasal or subcutaneous luteinizing hormone-releasing hormone agonist inhibition of ovarian function in the treatment of endometriosis. *Am J Obstet Gynecol* 1988; **158:** 233–6.
2. Donnez J, *et al.* Administration of nasal buserelin as compared with subcutaneous buserelin implant for endometriosis. *Fertil Steril* 1989; **52:** 27–30.
3. Nieto A, *et al.* Long term follow-up of endometriosis after two different therapies (gestrinone and buserelin). *Clin Exp Obstet Gynecol* 1996; **23:** 198–204.
4. Regidor P-A, *et al.* Long-term follow-up on the treatment of endometriosis with the GnRH-agonist buserelin acetate. *Eur J Obstet Gynecol Reprod Biol* 1997; **73:** 153–60.
5. Takeuchi H, *et al.* A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis. *J Obstet Gynaecol Res* 2000; **26:** 325–31.

Fibroids. Like other gonadorelin analogues (see also p. 2281.2) buserelin has been used to reduce the volume of uterine fibroids.

References.

1. Maheux R, *et al.* Use of intranasal luteinizing hormone-releasing hormone agonist in uterine leiomyomas. *Fertil Steril* 1987; **47:** 229–33.
2. Matta WHM, *et al.* Long-term follow-up of patients with uterine fibroids after treatment with the LHRH agonist buserelin. *Br J Obstet Gynaecol* 1989; **96:** 200–6.
3. Pedele L, *et al.* Intranasal buserelin versus surgery in the treatment of uterine leiomyomata: long-term follow-up. *Eur J Obstet Gynecol Reprod Biol* 1991; **38:** 53–7.
4. Ueki M, *et al.* Endocrinological and histological changes after treatment of uterine leiomyomas with danazol or buserelin. *J Obstet Gynaecol* 1995; **21:** 1–7.

Infertility. Buserelin is given with gonadotrophic hormone therapy for induction of ovulation and as an aid to improving IVF procedures. Buserelin with gonadotrophic hormones has been found to result in pregnancies in women previously unresponsive to clomifene citrate,[1,2] although there may be a greater risk of multiple births.[3]

The regimens used in IVF may be characterised according to how long the gonadorelin analogue is given for:

- long, 2 weeks or more
- short, 8 to 10 days
- ultrashort, 3 days

A comparative study of such regimens found that the best results in all age groups were consistently associated with the long buserelin protocol.[4] The timing of buserelin dosage may also be important. Starting buserelin in the midluteal phase of the cycle has been reported to produce more rapid pituitary down regulation and higher pregnancy rates from IVF than when buserelin was begun in the early follicular phase.[5]

For a general discussion of the management of infertility, see p. 2253.1.

1. Armitage M, *et al.* Successful treatment of infertility due to polycystic ovary disease using a combination of luteinising hormone releasing hormone agonist and low dosage menotrophin. *BMJ* 1987; **295:** 96.
2. Owen EJ, *et al.* The use of a short regimen of buserelin, a gonadotrophin-releasing hormone agonist, and human menopausal gonadotrophin in assisted conception cycles. *Hum Reprod* 1989; **4:** 749–53.
3. Rutherford AJ, *et al.* Improvement of in vitro fertilisation after treatment with buserelin, an agonist of luteinising hormone releasing hormone. *BMJ* 1988; **296:** 1765–8.
4. Tan S-L, *et al.* Cumulative conception and live-birth rates after in vitro fertilization with and without the use of long, short, and ultrashort regimens of the gonadotrophin-releasing hormone agonist buserelin. *Am J Obstet Gynecol* 1994; **171:** 513–20.
5. Urbancsek J, Witthaus E. Midluteal buserelin is superior to early follicular phase buserelin in combined gonadotropin-releasing hormone analog and gonadotropin stimulation in in vitro fertilization. *Fertil Steril* 1996; **65:** 966–71.

Malignant neoplasms. The long-term use of buserelin in men decreases the testicular concentration of testosterone. For this reason it is used in the treatment of prostatic cancer (p. 712.3), which is androgen-dependent.[1] Gonadorelin analogues are an effective alternative to orchidectomy, sometimes combined with an anti-androgen for enhanced effect, and play a major role in the management of advanced, incurable disease.

Other reports of malignant neoplasms treated with buserelin include its use in metastatic breast cancer[2,3] (p. 702.1).

1. de Voogt HJ, *et al.* The use of the LHRH-analogue buserelin in the treatment of prostatic cancer: a 10-year review on 1522 patients treated in 119 centers on 4 continents. *Scand J Urol Nephrol Suppl* 1991; 138: 131–6.
2. Falkson CI, *et al.* Cyclophosphamide, doxorubicin and fluorouracil (CAF) plus depo-buserelin in the treatment of premenopausal women with metastatic breast cancer. *Ann Oncol* 1992; 3: 849–53.
3. Klijn JG, *et al.* Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study. *J Natl Cancer Inst* 2000; 92: 903–11.

Porphyria. Buserelin given with medroxyprogesterone acetate suppressed cyclic and premenstrual exacerbations of porphyria (p. 1556.1) in 2 patients. Doses used were 300 micrograms buserelin intranasally in the evenings of days 1 to 21 of the menstrual cycle and 10 mg of oral medroxyprogesterone acetate daily from day 12 to 21. Both patients were free from porphyric attacks during the reported 11 months of treatment.[1] Intranasal buserelin has also been used in 1 patient to prevent premenstrual exacerbation of coproporphyria.[2] The initial dose of 900 micrograms daily could be tapered to 150 micrograms daily, with only 1 minor attack in 5 years of treatment. The authors of this report also noted several case reports of buserelin used in acute intermittent porphyria.

1. Bargetzi MJ, *et al.* Premenstrual exacerbations in hepatic porphyria: prevention by intermittent administration of an LH-RH agonist in combination with a gestagen. *JAMA* 1989; 261: 864.
2. Yamamori I, *et al.* Prevention of premenstrual exacerbation of hereditary coproporphyria by gonadotropin-releasing hormone analogue. *Intern Med* 1999; 38: 365–8.

Precocious puberty. The gonadorelin analogues have largely replaced other treatments in the management of central precocious puberty (p. 2254.1).

References to the use of buserelin.

1. Drop SLS, *et al.* The effect of treatment with an LH-RH agonist (buserelin) on gonadal activity growth and bone maturation in children with central precocious puberty. *Eur J Pediatr* 1987; 146: 272–8.
2. Cacciari E, *et al.* Long-term follow-up and final height in girls with central precocious puberty treated with luteinizing hormone-releasing hormone analogue nasal spray. *Arch Pediatr Adolesc Med* 1994; 148: 1194–9.
3. Juul A, *et al.* Serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 levels are increased in central precocious puberty: effects of two different treatment regimens with gonadotropin-releasing hormone agonists, without or in combination with an antiandrogen (cyproterone acetate). *J Clin Endocrinol Metab* 1995; 80: 3059–67.
4. Bertelloni S, *et al.* Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr* 1998; 157: 363–7.
5. Tuvemo T, *et al.* Suppression of puberty in girls with short-acting intranasal versus subcutaneous depot GnRH agonist. *Horm Res* 2002; 57: 27–31.

Premenstrual syndrome. For reference to the use of buserelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug treatment, see under Gonadorelin, p. 2281.3.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies buserelin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1] For the use of buserelin in the prevention of premenstrual exacerbations of acute porphyria, see above.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for Gonadorelin, p. 2282.2.

Pharmacokinetics

Buserelin is completely absorbed after subcutaneous injection and peak plasma concentrations occur about 1 hour after a dose. It accumulates in liver and kidneys as well as in the anterior pituitary. It is metabolised by tissue peptidases and is excreted in urine and bile as unchanged drug and metabolites. The half-life after injection is stated to be about 80 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Suprefact; *Austria*: Suprecur; Suprefact; *Belg.*: Suprefact; *Braz.*: Suprefact; *Canad.*: Suprefact; *Denm.*: Suprecur; Suprefact; *Fin.*: Suprecur; Suprefact; *Fr.*: Bigonist; Suprefact; *Ger.*: Metrelef; Profact; *Gr.*: Suprefact; *Hong Kong*: Suprecur; *Hung.*: Suprefact; *Irl.*: Suprecur; Suprefact; *Israel*: Suprefact; *Ital.*: Suprefact; *Jpn*: Suprecur; *Malaysia*: Suprefact; *Mex.*: Suprefact; *Neth.*: Suprefact; *Norw.*: Suprecur; Suprefact†; *NZ*: Suprefact; *Port.*: Suprefact; *S.Afr.*: Suprefact; *Singapore*: Suprefact; *Spain*: Suprefact; *Swed.*: Suprecur; Suprefact; *Switz.*: Suprefact†; *Thai.*: Suprefact; *Turk.*: Suprecur; Suprefact; *UK*: Suprecur; Suprefact; *Ukr.*: Buserin (Бусерин); Suprefakt Depo (Супрефакт Депо)†.

Cetrorelix Acetate *(BANM, USAN, rINNM)*

Acetato de cetrorelix, Cétrorélix, Acétate de cétrorélix, Acetato de cetrorelix, Cetrorelix-Acetat, D-20761, NS-75A, SB-075, (cetrorelix), SB-75 (cetrorelix), Цетрореликса Ацетат

N-Acetyl-3-(2-naphthyl)-D-alanyl-D-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-*N*⁵-carbamoyl-D-ornithyl-L-leucyl-L-arginyl-L-prolyl-D-alaninamide acetate

$C_{70}H_{92}ClN_{17}O_{14}$,$C_2H_4O_2$=1431.1 (cetrorelix)

CAS — 120287-85-6 (cetrorelix); 145672-81-7 (cetrorelix acetate)

ATC — H01CC02

ATC Vet — QH01CC02

UNII — W9YBL7GP4G

Uses and Administration

Cetrorelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist used as a component of ovarian stimulation regimens for assisted reproduction in infertility (p. 2253.1); it is used to prevent luteinising hormone surges and premature ovulation. It has also been tried in benign prostatic hyperplasia, malignant neoplasms of the prostate, endometriosis, and for uterine fibroids.

Cetrorelix is given by subcutaneous injection as the acetate; an intramuscular depot formulation containing cetrorelix embonate is in development.

For assisted reproduction, doses of cetrorelix acetate equivalent to cetrorelix 250 micrograms daily may be given either in the morning beginning on day 5 or 6 of ovarian stimulation or in the evening beginning on day 5, and continued until ovulation induction. Alternatively a single dose equivalent to 3 mg of cetrorelix may be given on day 7; if follicle growth does not allow ovulation induction within 4 days, additional doses of cetrorelix 250 micrograms once daily may be given until the day of ovulation induction.

References.

1. Gonzalez-Barcena D, *et al.* Treatment of uterine leiomyomas with luteinizing hormone-releasing hormone antagonist cetrorelix. *Hum Reprod* 1997; 12: 2028–35.
2. Comaru-Schally AM, *et al.* Efficacy and safety of luteinizing hormone-releasing hormone antagonist cetrorelix in the treatment of symptomatic benign prostatic hyperplasia. *J Clin Endocrinol Metab* 1998; 83: 3826–31.
3. Felberbaum RE, *et al.* Treatment of uterine fibroids with a slow-release formulation of the gonadotrophin releasing hormone antagonist cetrorelix. *Hum Reprod* 1998; 13: 1660–8.
4. Huirne JAF, Lambalk CB. Gonadotropin-releasing-hormone-receptor antagonists. *Lancet* 2001; 358: 1793–1803.
5. Ludwig M, *et al.* Use of GnRH antagonists in ovarian stimulation for assisted reproductive technologies compared to the long protocol: meta-analysis. *Arch Gynecol Obstet* 2001; 265: 175–82.
6. Rouliez R, *et al.* Depot GnRH agonist versus the single dose GnRH antagonist regimen (cetrorelix, 3 mg) in patients undergoing assisted reproduction treatment. *Reprod Biomed Online* 2003; 7: 185–9.
7. Griesinger G, *et al.* Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differences between agents? *Drugs* 2004; 64: 563–75.
8. Al-Inany HG, *et al.* Gonadotrophin-releasing hormone antagonists for assisted conception. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2006 (accessed 28/07/08).
9. Finas D, *et al.* Cetrorelix in the treatment of female infertility and endometriosis. *Expert Opin Pharmacother* 2006; 7: 2155–68.
10. Tur-Kaspa I, Ezcurra D. GnRH antagonist, cetrorelix, for pituitary suppression in modern, patient-friendly assisted reproductive technology. *Expert Opin Drug Metab Toxicol* 2009; 5: 1323–36.

Adverse Effects and Precautions

Transient reactions at the injection site, including erythema, pruritus, and swelling, may occur. Nausea and headache have been reported occasionally. Systemic hypersensitivity reactions have been reported rarely.

Cetrorelix should not be used in patients with moderate to severe renal or hepatic impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cetrorelix 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 06/10/11)

Pharmacokinetics

The bioavailability of cetrorelix after subcutaneous injection is about 85%. The mean terminal half-life after a subcutaneous injection of 3 mg is about 60 hours; it is less with lower doses (about 5 and 20 hours respectively after single and multiple doses of 250 micrograms).

References.

1. Pechstein B, *et al.* Pharmacokinetic-pharmacodynamic modeling of testosterone and luteinizing hormone suppression by cetrorelix in healthy volunteers. *J Clin Pharmacol* 2000; 40: 266–74.
2. Nagaraja NV, *et al.* Pharmacokinetic and pharmacodynamic modeling of cetrorelix, an LH-RH antagonist, after subcutaneous administration in healthy premenopausal women. *Clin Pharmacol Ther* 2000; 68: 617–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cetrotide; *Austral.*: Cetrotide; *Austria*: Cetrotide; *Belg.*: Cetrotide; *Braz.*: Cetrotide; *Canad.*: Cetrotide; *Chile*: Cetrotide†; *China*: Cetrotide (思则凯); *Cz.*: Cetrotide; *Denm.*: Cetrotide; *Fin.*: Cetrotide; *Fr.*: Cetrotide; *Ger.*: Cetrotide†; *Gr.*: Cetrotide; *Hong Kong*: Cetrotide; *Hung.*: Cetrotide; *India*: Cetrotide; Ovurelix; *Indon.*: Cetrotide; *Irl.*: Cetrotide; *Israel*: Cetrotide; *Ital.*: Cetrotide; *Malaysia*: Cetrotide; *Mex.*: Cetrotide; *Neth.*: Cetrotide; *Norw.*: Cetrotide; *NZ*: Cetrotide; *Philipp.*: Cetrotide; *Pol.*: Cetrotide; *Port.*: Cetrotide; *Rus.*: Cetrotide (Цетротид); *S.Afr.*: Cetrotide; *Singapore*: Cetrotide; *Spain*: Cetrotide; *Swed.*: Cetrotide; *Switz.*: Cetrotide; *Thai.*: Cetrotide; *Turk.*: Cetrotide; *UK*: Cetrotide; *USA*: Cetrotide; *Venez.*: Cetrotide.

Chlormadinone Acetate *(BANM, USAN, rINNM)*

Acetato de clormadinona, Chlormadinone, Acétate de chlormadinol, Acetas Clormadinona, acetato de, NSC-92338, Хлормадинона Ацетат

6-Chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate

$C_{23}H_{29}ClO_4$=404.9

CAS — 1961-77-9 (chlormadinone); 302-22-7 (chlormadinone acetate)

ATC — G03DB06

ATC Vet — QG03DB06

UNII — 05Y050L61N

Pharmacopoeias. In *Chin.*, *Fr.*, and *Jpn*.

Uses and Administration

Chlormadinone acetate is a progestogen structurally related to progesterone (p. 2300.2) that has anti-androgenic activity. It is given either alone or with an oestrogen in the treatment of menstrual disorders such as menorrhagia (p. 2300.3) and endometriosis (p. 2264.1) in oral doses of 2 to 10 mg daily either cyclically or continuously. It may also be used as the progestogen component of combined oral contraceptives (see p. 2231.3) at a dose of 1 to 2 mg daily, particularly in women with androgen-dependent conditions such as acne and hirsutism. Chlormadinone acetate has been used in some countries in the management of prostatic hyperplasia and prostate cancer; oral doses of 25 or 50 mg, respectively have been given twice daily.

Reviews.

1. Curran MP, Wagstaff AJ. Ethinylestradiol/chlormadinone acetate. *Drugs* 2004; 64: 751–60.
2. Bouchard P. Chlormadinone acetate (CMA) in oral contraception—a new opportunity. *Eur J Contracept Reprod Health Care* 2005; 10 (suppl 1): 7–11.
3. Schramm G, Heckes B. Switching hormonal contraceptives to a chlormadinone acetate-containing oral contraceptive: the Contraceptive Switch Study. *Contraception* 2007; 76: 84–90.
4. Druckmann R. Profile of the progesterone derivative chlormadinone acetate - pharmocodynamic [sic] properties and therapeutic applications. *Contraception* 2009; 79: 272–81.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Effects on the skin. A report of auto-immune dermatitis in a patient associated with chlormadinone acetate.[1]

1. Katayama I, Nishioka K. Autoimmune progesterone dermatitis with persistent amenorrhoea. *Br J Dermatol* 1985; 112: 487–91.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Luteran; *Jpn*: Prostal; *Mex.*: Lutoral.

Multi-ingredient Preparations. *Austria*: Balanca; Belara; Madinette; *Braz.*: Belara; *Chile*: Belara; Gynorelle; Lovinda; *Cz.*: Belara; Clormetin; Egretta; Esete; Larabel†; Madinelle; *Fr.*: Belara; *Ger.*: Balanca†; Belara; Bellissima; Chariva; Enriqa; Estiria†; Madinette; Minette; Neo-Eunomin; Pink Luna; Verana; *Hung.*: Belara; *Israel*: Belara; *Ital.*: Belara; Lybella; *Mex.*: Belara; Lutoral-E; Secuentex-21; *Pol.*: Madinette; *Port.*: Belara; Libeli; *Rus.*: Belara (Белара); *Spain*: Balanca; Belara; Elynor; *Switz.*: Belara; Belarina; Ladonna; Madinette; Tyarena; *Thai.*: Belara; *Turk.*: Belara; *Ukr.*: Belara (Белара); *Venez.*: Belara.

Chlorotrianisene (BAN, rINN)

Chlorotrianisène; Chlorotrianisenum; Clorotrianiseno; Kloortrianiseeni; Klortrianisen; NSC-10108; Tri-*p*-anisylchloroethylene; Хлоротрианизен.

Chlorotris(4-methoxyphenyl)ethylene.

$C_{23}H_{21}ClO_3$=380.9

CAS — 569-57-3.

ATC — G03CA06.

ATC Vet — QG03CA06.

UNII — 6V5034L121.

Pharmacopoeias. In *Chin.*

Profile

Chlorotrianisene is a synthetic nonsteroidal oestrogen structurally related to diethylstilbestrol (p. 2267.3). It has a prolonged action, and has been given orally for the treatment of menopausal symptoms, female hypogonadism, and prostatic carcinoma.

Chorionic Gonadotrophin

(BAN, rINN) ⊗

CG; Choriogonadotrophin; Chorionic Gonadotropin; Chorioninis gonadotropinas; Coriogonadotrofina; Coriogonadotropina; Gonadotrofina coriónica; Gonadotrofina coriónica humana; Gonadotrophine Chorionique; Gonadotrophinum Chorionicum; Gonadotropin choriový; Gonadotropina coriónica; Gonadotropina coriónica humana; Gonadotropine chorionique; Gonadotropinum Chorionicum; HCG; Human Chorionic Gonadotrophin; Koriongonadotroplini; Korion-gonadotropin; Koriongonadotropin; Koriyonik Gonadotrofin; Pregnancy-urine Hormone; PU; Гонадотропин Хорионический.

CAS — 9002-61-3.

ATC — G03GA01.

ATC Vet — QG03GA01.

UNII — 20ED16GHEB (human chorionic gonadotrophin).

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

Ph. Eur. 8: (Gonadotrophin, Chorionic). A dry preparation of placental glycoproteins extracted from the urine of pregnant women. The potency is not less than 2500 units/mg. A white to yellowish-white, amorphous powder. Soluble in water. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Chorionic Gonadotropin). A gonad-stimulating polypeptide hormone obtained from the urine of pregnant women. It has a potency of not less than 1500 USP units/mg. A white or practically white, amorphous powder. Freely soluble in water. Store in airtight containers at 2 degrees to 8 degrees.

Choriogonadotropin Alfa (BAN, USAN, rINN) ⊗

Choriogonadotropine Alfa; Choriogonadotropinum Alfa; Coriogonadotropina alfa; Хориогонадотропин Альфа.

CAS — 177073-44-8 (choriogonadotropin alfa); 56832-30-5 (α subunit); 56832-34-9 (β subunit).

ATC — G03GA08.

ATC Vet — QG03GA08.

UNII — 6413W06WR3.

Uses and Administration

Chorionic gonadotrophin is a hormone produced by the placenta and obtained from the urine of pregnant women. Its effects are mainly those of the gonadotrophin, luteinising hormone (p. 2287.1), which is responsible for triggering ovulation and formation of the corpus luteum in women, and stimulates the production of testosterone by the testes in men. It is usually given by intramuscular injection although the subcutaneous route has also been used. Choriogonadotropin alfa is a recombinant form of chorionic gonadotrophin.

In *women* with **anovulatory infertility** due to absent or low concentrations of gonadotrophins, chorionic gonadotrophin is given to induce ovulation after follicular development has been stimulated with follicle-stimulating hormone or human menopausal gonadotrophins. A single dose of 5000 to 10 000 units of chorionic gonadotrophin is given by intramuscular injection to mimic the midcycle peak of luteinising hormone which normally stimulates ovulation. Chorionic gonadotrophin is also used with follicle stimulation as an adjunct to IVF procedures and other assisted conception techniques involving superovulation and oocyte collection. A further 2 or 3 injections of 1000 to 3000 units may be given for luteal support in the 9 days after ovulation or embryo transfer.

Choriogonadotropin alfa is used similarly to induce ovulation in the treatment of anovulatory infertility, or as an adjunct to IVF procedures and other assisted conception techniques. A single dose of 250 micrograms is given, by subcutaneous injection, when optimal stimulation of follicular growth is achieved.

Chorionic gonadotrophin is also given for *male* infertility associated with hypogonadotrophic **hypogonadism**. There is considerable variation between dosage regimens, and doses have ranged from 500 to 4000 units two or three times weekly by intramuscular injection. A drug with follicle-stimulating activity such as menotrophin is often added to enable normal spermatogenesis.

For the use of chorionic gonadotrophin in children, see below.

Administration in children. Chorionic gonadotrophin may be used in various conditions in boys, including cryptorchidism and delayed puberty, and in tests of testicular function (see below).

Cryptorchidism. Although surgery remains the treatment with the best success rate, primary hormonal therapy with chorionic gonadotrophin is widely used for cryptorchidism (p. 2252.1). Systematic reviews[1,2] suggest a success rate of about 20% overall, although this may be reduced when care is taken to exclude retractile testes. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, which may act as a predictor of future fertility.[3] Chorionic gonadotrophin may also be used as an adjuvant before surgery, to render the testes palpable,[4] but changes suggestive of inflammation in the testis have been reported after such treatment.[5]

Treatment should be given before puberty. The dose of chorionic gonadotrophin will depend on weight and age, and recommended regimens vary widely between different licensed products as well as clinical guidelines. In general, doses may range from 500 to 4000 units three times weekly by intramuscular injection, and may be given for 3 to 6 weeks or possibly longer.

1. Pyörälä S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; **80**: 2795–9.
2. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; **20**: 357–9.
3. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (update March 2009). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Paediatric_Urology.pdf (accessed 23/10/09)
4. Polascik TJ, *et al.* Reappraisal of the role of human chorionic gonadotropin in the diagnosis and treatment of the nonpalpable testis: a 10-year experience. *J Urol (Baltimore)* 1996; **156**: 804–6.
5. Kaleva M, *et al.* Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. *Int J Androl* 1996; **19**: 293–8.

Delayed puberty. Use of chorionic gonadotrophin may be appropriate in boys with delayed puberty due to hypogonadotrophic hypogonadism (p. 2252.1). An initial dose of 500 units may be given twice weekly by intramuscular injection, and the dose should be titrated against the plasma-testosterone concentration. Doses up to 1500 units twice weekly for at least 6 months may be used.

Infertility. In women with anovulatory infertility chorionic gonadotrophin and choriogonadotropin alfa can be used to provoke ovulation and provide luteal support once maturation of a suitable number of follicles has been stimulated by other means. They are used similarly in the various protocols for assisted reproduction. However, use is not recommended for assisted reproduction in patients at risk of ovarian hyperstimulation, such as those with polycystic ovary syndrome. In men with hypogonadotrophic hypogonadism chorionic gonadotrophin is used to stimulate and maintain spermatogenesis. The management of male and female infertility, including the role of chorionic gonadotrophin, is discussed on p. 2253.1.

Malignant neoplasms. Control of Kaposi's sarcoma (p. 718.1) has been reported in a few patients given high-dose intramuscular chorionic gonadotrophin, but regrowth occurred when dosage was reduced or withdrawn.[1] Another study, using lower doses, was stopped due to toxicity and lack of benefit,[2] but others have confirmed benefit after intralesional injection.[3] There is some suggestion that preparations vary in their activity against the tumour and that it is not chorionic gonadotrophin itself, but some impurity (perhaps a ribonuclease[4] or the degradation product of the β-subunit[5]), that is the active principle.[3,6,7] Some contaminants may have a stimulant effect on the neoplasm, which might also contribute to the variable results.[5]

1. Harris PJ. Treatment of Kaposi's sarcoma and other manifestations of AIDS with human chorionic gonadotropin. *Lancet* 1995; **346**: 118–19.
2. Bower M, *et al.* Human chorionic gonadotropin for AIDS-related Kaposi's sarcoma. *Lancet* 1995; **346**: 642.
3. Gill PS, *et al.* The effects of preparations of human chorionic gonadotropin on AIDS-related Kaposi's sarcoma. *N Engl J Med* 1996; **335**: 1261–9. Correction. *ibid.* 1997; **336**: 1115.
4. Griffiths SJ, *et al.* Ribonuclease inhibits Kaposi's sarcoma. *Nature* 1997; **390**: 568.
5. Simonart T, *et al.* Treatment of Kaposi's sarcoma with human chorionic gonadotropin. *Dermatology* 2002; **204**: 330–3.
6. Gill PS, *et al.* Intralesional human chorionic gonadotropin for Kaposi's sarcoma. *N Engl J Med* 1997; **336**: 1188.
7. von Overbeck J, *et al.* Human chorionic gonadotropin for AIDS-related Kaposi's sarcoma. *Lancet* 1995; **346**: 642–3.

Obesity. A meta-analysis[1] involving 24 studies concluded that there was no evidence that chorionic gonadotrophin was effective in the treatment of obesity (p. 2315.1).

1. Lijesen GKS, *et al.* The effect of human chorionic gonadotropin (HCG) in the treatment of obesity by means of the Simeons therapy: a criteria-based meta-analysis. *Br J Clin Pharmacol* 1995; **40**: 237–43.

Testicular function. Chorionic gonadotrophin is used in the assessment of testicular function in suspected primary hypogonadism and incomplete masculinisation. Although unlicensed for this use in the UK, the *BNFC* states that for children aged 1 month to 18 years a dose of 1500 to 2000 units may be given intramuscularly once daily for 3 days (short stimulation test) or twice weekly for 3 weeks (prolonged test).

Adverse Effects and Precautions

Adverse effects that have been reported with chorionic gonadotrophin include headache, tiredness, changes in mood, depression, restlessness, oedema (especially in males), and pain on injection. Treatment for cryptorchidism may produce premature epiphyseal closure or precocious puberty. Gynaecomastia has been reported. Ovarian hyperstimulation may occur, with marked ovarian enlargement or cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock, and thromboembolic disorders in severe cases.

Chorionic gonadotrophin should be given with care to patients in whom androgen-induced fluid retention might be a hazard as in asthma, epilepsy, migraine, or cardiovascular disorders, including hypertension, or renal disorders. Hypersensitivity reactions may occur and it is recommended that patients suspected to be susceptible should be given skin tests before treatment. It should not be given to patients with disorders that might be exacerbated by androgen release such as carcinoma of the prostate or precocious puberty. Use should also be avoided in the presence of breast, uterine, ovarian, and testicular tumours, as well as tumours of the hypothalamus, pituitary, thyroid, and adrenal glands.

Pharmacokinetics

Peak concentrations of chorionic gonadotrophin occur about 6 hours after an intramuscular dose and 16 to 20 hours after a subcutaneous injection. It is distributed mainly to the gonads. Blood concentrations decline in a biphasic manner, with half-lives of about 6 to 11 hours and 23 to 38 hours, respectively. Chorionic gonadotrophin is metabolised mainly in the kidneys. About 10 to 12% of an intramuscular dose is excreted in urine within 24 hours.

After subcutaneous doses, choriogonadotropin alfa has a bioavailability of about 40%. It is metabolised and excreted similarly to chorionic gonadotrophin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dinaron; Endocorion; Gonacor; Ovidrel; Pregnyl; *Austral.*: Ovidrel; Pregnyl; Profasi†; *Austria*: Ovitrelle; Pregnyl; *Belg.*: Choragon; Ovitrelle; Pregnyl; *Braz.*: Choriomon; Ovidrel; Pregnyl; Profasi HP†; *Canad.*: Ovidrel; Pregnyl; Profasi HP†; *Chile*: Gonacor; Ovidrel; Pregnyl; *China*: Ovidrel (艾泽); Pregnyl (波热尼乐); *Cz.*: Ovitrelle; Pregnyl; *Denm.*: Ovitrelle; Pregnyl; *Fin.*: Ovitrelle; Pregnyl; *Fr.*: Ovitrelle; *Ger.*: Brevactid; Choragon†; Ovitrelle; Predalon; *Gr.*: Ovitrelle; Pregnyl; Profasi; *Hong Kong*: Choragon; Ovidrel; Pregnyl; Profasi†; *Hung.*: Choragon; Ovitrelle; Pregnyl; *India*: Choragon; Choriolife; Choriomon; Corion; Corlova; Fergonad-C; Fertigyn; Huchogon; Hucog; Humunis; LG IVF-C; Materna HCG; Origin; Ovidac; Ovidrel; Ovulate-C; Ovumax-HP; Ovutrig-HP; Profasi; Proligon; Provigil; Pubergen; *Indon.*: Ovidrel; Pregnyl; *Irl.*: Ovitrelle; Pregnyl; Profasi†; *Israel*: Ovitrelle; Pregnyl; *Ital.*: Gonasi HP; Ovitrelle; Pregnyl; *Malaysia*: Choragon†; Ovidrel; Pregnyl; *Mex.*: Choragon; Choriomon; Ovidrel; Pregnyl; *Neth.*: Choragon; Ovitrelle; Pregnyl; *Norw.*: Ovitrelle; Pregnyl; *NZ*: Ovidrel; Pregnyl; Profasi; *Philipp.*: Ovidrel; Pregnyl; *Pol.*: Choragon; Ovitrelle; Pregnyl; *Port.*: Ovitrelle; Pregnyl; *Rus.*: Choragon (Хорагон); Ecostimulin (Экостимулин); Ovitrelle (Овитрель); Pregnyl (Прегнил); *S.Afr.*: APL†; Ovidrel; Pregnyl; Profasi; *Singapore*: Ovidrel; Pregnyl; Profasi; *Spain*: Ovitrelle; *Swed.*: Ovitrelle; Pregnyl; *Switz.*: Choriomon; Ovitrelle; Pregnyl; *Thai.*: IVF-C; Ovidrel; Pregnyl; *Turk.*: Choragon; Ovitrelle; Pregnyl; Profasi; *UK*: Choragon; Ovitrelle; Pregnyl; *Ukr.*: Choragon (Хорагон); Pregnyl (Прегнил); *USA*: Choron†; Gonic†; Novarel; Ovidrel; Pregnyl; Profasi†; *Venez.*: Ovidrel; Pregnyl.

Multi-ingredient Preparations. *Mex.*: Gonakor.

Pharmacopoeial Preparations

BP 2014: Chorionic Gonadotrophin Injection;
USP 36: Chorionic Gonadotropin for Injection.

Clomifene Citrate (BANM, rINNM) ⊗

Chloramiphene Citrate; Citrato de clomifeno; Citrato de cloramifeno; Clomifenactrati; Clomifène, citrate de; Clomifeni citras; Clomifenol citrato de; Clomiphene Citrate (USAN); Clomifenie Citrate; Kloomifeenisitraatti; Klomifen sitrat; Klomifenitrat; Klomifen citrat; Klomifen citrat; Klomifeno citratas; MER-41; MRL-41; NSC-35770; Кломифена Цитрат

A mixture of the *E* and *Z* isomers of 2-[4-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine dihydrogen citrate.

$C_{26}H_{28}ClNO,C_6H_8O_7$ = 598.1

CAS — 911-45-5 (clomifene); 15690-57-0 (*E*-clomifene); 15690-55-8 (*Z*-clomifene); 50-41-9 (clomifene citrate); 7599-79-3 (*E*-clomifene citrate); 7619-53-6 (*Z*-clomifene citrate)

ATC — G03CB02

ATC Vet — QG03CB02

UNII — 88447E7Y (clomifene citrate); UY5X264QZV (*Z*-clomifene citrate)

NOTE. Clomifene may be separated into its *Z*-and *E*-isomers, zuclomifene and enclomifene.

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

Ph. Eur. 8: (Clomifene Citrate). A white or pale yellow, crystalline powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Clomiphene Citrate). A white to pale yellow, essentially odourless powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water and in chloroform; sparingly soluble in alcohol; insoluble in ether; freely soluble in methyl alcohol.

Uses and Administration

Clomifene is a nonsteroidal compound that has both oestrogenic and anti-oestrogenic properties, the latter residing mainly in the *E*-isomer. Its action in stimulating ovulation is believed to be related to its anti-oestrogenic properties. It stimulates the secretion of pituitary gonadotrophic hormones, probably by blocking the negative feedback effect of oestrogens at receptor sites in the hypothalamus and pituitary.

Clomifene is used in the treatment of anovulatory infertility (p. 2253.1). Therapy with clomifene will not be successful unless the woman, though anovulatory, is capable of ovulation and her partner is fertile. It is ineffective in primary pituitary or primary ovarian failure. The usual oral dose is 50 mg of clomifene citrate daily for 5 days, starting on or about the fifth day of the menstrual cycle or at any time if there is amenorrhoea. Ovulation is expected to occur about 5 to 10 days after a course of clomifene, and coitus should be timed to coincide with this. If ovulation does not occur, a course of 100 mg daily for 5 days may be given starting as early as 30 days after the previous one. Women should be examined for pregnancy and ovarian enlargement or cysts between treatment cycles. In general, 3 courses of therapy are adequate to assess whether ovulation is obtainable. If ovulation has not occurred, the diagnosis should be re-evaluated. Once ovulation is established, each treatment cycle of clomifene should be started on or about the fifth day of the menstrual cycle. If pregnancy has not occurred within 3 ovulatory cycles, further treatment is not recommended. A maximum of 6 cycles in total is generally advised (see also Carcinogenicity, below).

Clomifene has been used in the treatment of male infertility due to oligospermia to stimulate gonadotrophin release and enhance spermatogenesis, but there is limited convincing evidence of benefit.

Infertility. Reviews.

1. Homburg R. Clomiphene citrate—end of an era? a mini-review. *Hum Reprod* 2005; 20: 2043–51.
2. Cédrin-Durnerin I. Contre l'utilisation du citrate de clomifène dans les infertilités inexpliquées. *Gynecol Obstet Fertil* 2006; 34: 61–5.
3. Merviel P. Pour une utilisation raisonnable du citrate de clomifène dans les infertilités inexpliquées. *Gynecol Obstet Fertil* 2006; 34: 66–9.
4. The Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in women. *Fertil Steril* 2006; 86 (5 suppl): S187–S193.

Adverse Effects

The incidence and severity of adverse effects of clomifene citrate tend to be related to the dose used. The most commonly reported adverse effects are reversible ovarian enlargement and cyst formation, vasomotor flushes resembling menopausal symptoms, and abdominal or pelvic discomfort or pain, sometimes with nausea or vomiting. Ovarian hyperstimulation syndrome has occurred. Breast tenderness, abnormal uterine bleeding, weight gain, headache, and endometriosis have also been reported. Transient visual disturbances such as spots or flashes, after-images, and blurring of vision may occur, and there have been rare reports of cataracts and optic neuritis. Skin reactions such as allergic rashes and urticaria have occasionally been reported and reversible hair loss has been reported rarely. CNS disturbances have included convulsions, dizziness, lightheadedness, nervous tension, fatigue, vertigo, insomnia, and depression. Abnormalities in liver function tests and jaundice have sometimes been reported.

There is an increased risk of multiple births with clomifene therapy, but rarely more than twins. There is also an increased risk of ectopic pregnancy. Although there have been reports of congenital disorders such as neural tube defects or Down's syndrome in infants born to women treated with clomifene, the role of the drug in the causation of these defects has not been established and the incidence is reported to be similar to that for the general population.

Carcinogenicity. There have been several reports suggesting an association between drug therapy to treat infertility by stimulating ovulation and the subsequent development of ovarian cancer.[1-5] Concern has focused in particular on the use of clomifene citrate and gonadotrophins, and a study has reported an increased risk of ovarian cancer in women who had prolonged clomifene therapy (for one year or more) although not in those who received the drug for a shorter period.[6] No association between gonadotrophin therapy and ovarian cancer was noted in this study. The conclusions of this study were only tentative, since the numbers who developed ovarian cancer were small; it has been pointed out that a successfully achieved pregnancy may reduce the risk of some other cancers, and that the risks and benefits of the procedure are not easy to balance.[7] A review[8] of epidemiological and cohort studies concluded that clomifene was not associated with any increase in the risk of ovarian cancer when used for less than 12 cycles, but noted conflicting results, limitations of the data, and the need to control for infertility and nulliparity as risk factors for ovarian cancer. Further cohort[9,10] and case-control[11] studies, and pooled analyses,[12,13] have also found no association between use of clomifene and ovarian cancer.

As a matter of prudence the UK CSM has recommended that clomifene should not normally be used for more than 6 cycles.[14] UK guidelines on the management of infertility[15] also recommend that clomifene should be used for a maximum of 6 months.

1. Fishel S, Jackson P. Follicular stimulation for high tech pregnancies: are we playing it safe? *BMJ* 1989; 299: 309–11.
2. Kulkarni R, McGarry JM. Follicular stimulation and ovarian cancer. *BMJ* 1989; 299: 740.
3. Dietl J. Ovulation and ovarian cancer. *Lancet* 1991; 338: 445.
4. Willemsen W, *et al.* Ovarian stimulation and granulosa-cell tumour. *Lancet* 1993; 341: 986–8.
5. Seward K, *et al.* Fertility drugs and malignant germ-cell tumour of ovary in pregnancy. *Lancet* 1998; 351: 957–8.
6. Rossing MA, *et al.* Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994; 331: 771–6.
7. Whittemore AS. The risk of ovarian cancer after treatment for infertility. *N Engl J Med* 1994; 331: 805–6.
8. Duckitt K, Templeton AA. Cancer in women with infertility. *Curr Opin Obstet Gynecol* 1998; 10: 199–203.
9. Potashnik G, *et al.* Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. *Fertil Steril* 1999; 71: 853–9.
10. Brinton LA, *et al.* Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstet Gynecol* 2004; 103: 1194–1203.
11. Rossing MA, *et al.* A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol* 2004; 160: 1070–8.
12. Ness RB, *et al.* Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2002; 155: 217–24.
13. Kashyap S, *et al.* Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis. *Obstet Gynecol* 2004; 103: 785–94.
14. CSM/MCA. Clomiphene (Clomid, Serophene): possible association with ovarian cancer. *Current Problems* 1995; 21: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 30/06/08)
15. NICE. Fertility: assessment and treatment for people with fertility problems (issued February 2013). Available at: http://www.nice.org.uk/nicemedia/live/14078/62769/62769.pdf (accessed 30/10/13)

Effects on the CNS. An infertile woman had convulsions when given clomifene citrate;[1] only 5 other cases had been reported since 1963.

1. Rimmington MR, *et al.* Convulsions after clomiphene citrate. *BMJ* 1994; 309: 512.

Effects on the eyes. As mentioned above, clomifene may cause visual disturbances, which resolve on stopping treatment. However, visual symptoms have persisted in a few cases.[1]

1. Purvin VA. Visual disturbance secondary to clomiphene citrate. *Arch Ophthalmol* 1995; 113: 482–4.

Effects on the fetus. After reports of neural tube defects in fetuses conceived after ovulation induction, analyses of congenital defect registers and follow-up studies of clomifene use suggested that the drug might possibly be associated with an increase in risk.[1-5] However, subsequent studies reported no increased risk[6-8] and a pooled analysis[9] of 10 epidemiological studies found no strong evidence to confirm an association. Further studies have also reported no increased risk of neural tube defects[10] or hypospadias in male offspring[11] after exposure to fertility treatment. However, another case-control study[12] did find a potential association between clomifene and neural tube defects, but noted that because of the low baseline prevalence of the malformation, the absolute risk difference would be small. It is not clear whether the underlying infertility itself affects the risk of congenital defects and whether it may confound the calculated risk associated with clomifene.[9]

1. Cornel MC, *et al.* Ovulation induction and neural tube defects. *Lancet* 1989; i: 1386.
2. Czeizel A. Ovulation induction and neural tube defects. *Lancet* 1989; ii: 167.
3. Cuckle H, Wald N. Ovulation induction and neural tube defects. *Lancet* 1989; ii: 1281.
4. Cornel MC, *et al.* Ovulation induction, in-vitro fertilisation, and neural tube defects. *Lancet* 1989; ii: 1530.
5. Vollset SE. Ovulation induction and neural tube defects. *Lancet* 1990; 337: 178.
6. Mills JL, *et al.* Risk of neural tube defects in relation to maternal fertility and fertility drug use. *Lancet* 1990; 336: 103–4.
7. Rosa F. Ovulation induction and neural tube defects. *Lancet* 1990; 336: 1327.
8. Werler MM, *et al.* Ovulation induction and risk of neural tube defects. *Lancet* 1994; 344: 445–6.
9. Greenland S, Ackerman DL. Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. *Fertil Steril* 1995; 64: 936–41.
10. Whiteman D, *et al.* Reproductive factors, subfertility, and risk of neural tube defects: a case-control study based on the Oxford Record Linkage Study Register. *Am J Epidemiol* 2000; 152: 823–8.
11. Sørensen HT, *et al.* Use of clomifene during early pregnancy and risk of hypospadias: population based case-control study. *BMJ* 2005; 330: 126–7.
12. Wu YW, *et al.* Potential association between infertility and spinal neural tube defects in offspring. *Birth Defects Res A Clin Mol Teratol* 2006; 76: 718–22.

Effects on mental function. Acute psychotic reactions with paranoid tendencies have occurred rarely during clomifene use.[1,2]

1. Siedentopf F, *et al.* Clomiphene citrate as a possible cause of a psychotic reaction during infertility treatment. *Hum Reprod* 1997; 12: 706–7.
2. Oyffe I, *et al.* Clomiphene-induced psychosis. *Am J Psychiatry* 1997; 154: 1169–70.

Precautions

Clomifene is contra-indicated in patients with liver disease or a history of liver dysfunction. It should not be used in pregnancy. Clomifene should not be used in women with uterine bleeding that is undiagnosed or caused by hormone-dependent tumours, or in patients with pre-existing mental depression or thrombophlebitis because of the risk of exacerbation. Patients should be warned of the possibility of multiple births.

Clomifene should not be given to women with ovarian cysts, except those with polycystic ovary syndrome, and the lowest doses possible should be used to minimise ovarian enlargement or cyst formation; some patients with polycystic ovary syndrome may have an exaggerated response to usual doses of clomifene. Patients should be instructed to report any abdominal or pelvic pain, distension, or weight gain, as this may indicate the presence or enlargement of ovarian cysts. They should also be evaluated for the presence of ovarian cysts before each cycle of treatment. If abnormal enlargement occurs, clomifene should not be given until the ovaries have returned to pre-treatment size, and subsequent doses should be reduced. Clomifene should be used with caution in patients with uterine fibroids, due to the potential for enlargement of the fibroids.

Treatment should be stopped if visual disturbances develop and the patient warned that this might affect their ability to drive or operate machinery. Long-term cyclic therapy is not recommended, because of the uncertainty regarding increased risk of ovarian cancer, and a maximum of 6 cycles of treatment is generally advised (see also Carcinogenicity, above).

Pharmacokinetics

Clomifene citrate is absorbed from the gastrointestinal tract. It is metabolised in the liver and slowly excreted via the bile. Unchanged drug and metabolites are excreted in the faeces. The biological half-life is reported to be 5 days although traces are found in the faeces for up to 6 weeks. Enterohepatic recirculation takes place. The *E*-isomer is reported to be less well absorbed and more rapidly eliminated than the *Z*-isomer.

References.

1. Szuru M, *et al.* Pharmacokinetics of intravenous clomiphene isomers. *Br J Clin Pharmacol* 1989; 27: 639–40.
2. Ghobadi C, *et al.* Single-dose pharmacokinetic study of clomiphene citrate isomers in anovular patients with polycystic ovary disease. *J Clin Pharmacol* 2009; 49: 147–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Genozym; Serofene; Tocofeno; *Austral.*: Clomhexal†; Clomid; Fermil†; Serophene; *Belg.*:

Clomid; Pergotime; *Braz.*: Clomid; Indux; Serophene; *Canad.*: Clomid; Serophene; *Chile*: Serophene; Zimaquin; *China*: Fertilan (法地兰); *Cz.*: Clomhexal†; Clostilbegyt; *Denm.*: Pergotime; *Fin.*: Clomifen; *Fr.*: Clomid; Pergotime; *Ger.*: Clomhexal†; *Gr.*: Serpafar; *Hong Kong*: Clostilbegyt; Fertilan; Ova-Mit†; Serophene; *Hung.*: Clostilbegyt; *India*: Clofert; Clomidac; Clomiriv; Clomit; Clopreg; Clowin; Pertifact; Fertik; Fertomid; Ferton; Fertova; Fetrop; Folistim; Pulfyn; Mephy; Omicite; Ovipreg; Ovitec; Ovobel; Ovofar; Ovuclom; Siphene; *Indon.*: Blesifen; Clomifil†; Clovertil†; Dipthen; Pensipros; Fertilphen; Fertin; Genoclom; Mestrolin†; Ofertil; Pinfetil; Profertil; Provula; *Irl.*: Clomid; *Israel*: Ikaclomin; *Ital.*: Clomid; Prolifen; Serofene; *Malaysia*: Clomid; Clostilbegyt; Duinum; Ova-Mit; Ovinum; Phenate; *Mex.*: Omifin; *Neth.*: Clomid; Serophene†; *Norw.*: Pergotime; *NZ*: Phenate†; Serophene; *Philipp.*: Clomene; Clomid; Clostil; Ferticlo; Fertyl; I-Clom; Ova-Mit; Ovulet; Ovulin; *Pol.*: Clostilbegyt; *Port.*: Dufine; *Rus.*: Clostilbegyt (Клостилбегит); *S.Afr.*: Clomid; Clomihexal; Fertomid; *Singapore*: Clomid; Clostilbegyt; Duinum; Ova-Mit; Ovinum; Phenate; Proferril; Serophene; Sunophene; *Spain*: Omifin; *Swed.*: Pergotime; *Switz.*: Clomid†; Serophene; *Thai.*: Clomid; Duinum; Ova-Mit; Ovinum; Serophene; *Turk.*: Fertilin; Gonaphene; Klomen; Serophene; *UK*: Clomid; *Ukr.*: Clostilbegyt (Клостилбегит); *USA*: Clomid; Serophene; *Venez.*: Serophene.

Multi-ingredient Preparations. *India*: Ovipro-MF.

Pharmacopoeial Preparations
BP 2014: Clomifene Tablets;
USP 36: Clomiphene Citrate Tablets.

Clostebol Acetate *(BAN, rINNM)* ⊗

Acetato de clostebol; 4-Chlorotestosterone Acetate; Chlortestosterone Acetate; Clostébol, Acétate de; Clostebol, acetato de; Closteboli Acetas; Клостебола Ацетат.

4-Chloro-3-oxoandrost-4-en-17β-yl acetate; 4-Chloro-17β-hydroxyandrost-4-en-3-one acetate.

$C_{21}H_{29}ClO_3$=364.9

CAS — 1093-58-9 (clostebol); 855-19-6 (clostebol acetate).

UNII — 780ZZX4P14.

Profile

Clostebol acetate has anabolic properties (see Testosterone, p. 2305.1) and has been given by intramuscular injection and orally. It has also been applied topically to wounds and ulcers, and has been used as an ophthalmological preparation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Trofodermin†.

Multi-ingredient Preparations. *Braz.*: Clostemin; Novaderm; Trofodermin; *Chile*: Trofodermin Neomicina†; *Ital.*: Trofodermin; *Mex.*: Neobol.

Conjugated Oestrogens

Conjugated Estrogens; Estrogeenit, konjugoidut; Estrogena Coniugata; Estrogenai, konjuguoti; Estrogener, konjugerade; Estrogènes conjugués; Estrogeni Coniuncti; Estrogeni Coniuncti; Estrógenos conjugados; Estrogeny konjugované; Konjugált ösztrogének; Konjúge Östrojen; Эстрогены Конъюгированные.

ATC — G03CA57.

ATC Vet — QG03CA57.

UNII — IUSQR144QX (conjugated oestrogens); 8CC9ET5H86 (sodium 17β-dihydroequilin sulfate).

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

Ph. Eur. 8: (Estrogens, Conjugated). A mixture of various conjugated forms of oestrogens obtained from the urine of pregnant mares or by synthesis, dispersed in a suitable powdered diluent. It contains two principal components, 52.5 to 61.5% of sodium estrone sulfate and 22.5 to 30.5% of sodium equilin sulfate; the total of the combined two is 79.5 to 88.0%. It also contains 2.5 to 9.5% of sodium 17α-estradiol sulfate, 13.5 to 19.5% of sodium 17α-dihydroequilin sulfate, and 0.5 to 4.0% of sodium 17β-dihydroequilin sulfate. All percentages are related to the labelled content.

An almost white brownish amorphous powder.

USP 36: (Conjugated Estrogens). A mixture of sodium estrone sulfate and sodium equilin sulfate, derived wholly or in part from equine urine or synthetically from estrone and equilin. It contains other conjugated oestrogenic substances of the type excreted by pregnant mares. It contains 52.5 to 61.5% of sodium estrone sulfate and 22.5 to 30.5% of sodium equilin sulfate; the total of the two combined should comprise 79.5 to 88.0% of the labelled content of conjugated oestrogens. It should contain, as sulfate conjugates, 13.5 to 19.5% of 17α-dihydroequilin, 2.5 to 9.5% of 17α-estradiol, and 0.5 to 4.0% of 17β-dihydroequilin, relative to the labelled content of conjugated oestrogens.

If it is obtained from natural sources it is a buff-coloured amorphous powder which is odourless or has a slight characteristic odour; the synthetic form is a white to light buff-coloured crystalline or amorphous powder, odourless or with a slight odour. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Synthetic Conjugated Estrogens, A

Synthetic Conjugated Oestrogens, A; Синтетические Конъюгированные Эстрогены, А.

UNII — JM2621P2LS.

Synthetic Conjugated Estrogens, B *(USAN)*

CE-10; Synthetic Conjugated Oestrogens, B; Синтетические Конъюгированные Эстрогены, В.

CAS — 746658-13-9.

UNII — 8L6LAK9BTR.

Uses and Administration

Conjugated oestrogens have actions and uses similar to those described for estradiol (see p. 2271.2).

When used as menopausal HRT (p. 2244.2) doses of 0.3 to 1.25 mg daily are given orally either cyclically or continuously; in women with a uterus a progestogen is also given either cyclically or continuously. Doses of 0.3 to 1.25 mg may also be used for the prevention of postmenopausal osteoporosis, but oestrogen therapy is generally reserved for women who are at significant risk and who cannot be given non-hormonal treatment. Topical vaginal therapy may be used specifically for menopausal atrophic vaginitis, atrophic urethritis, and kraurosis vulvae; 0.5 to 2 g of a 0.0625% cream may be used daily for 3 weeks of a 4-week cycle. For moderate to severe dyspareunia associated with menopausal vulvar and vaginal atrophy, a topical vaginal dose of 0.5 g may be used twice weekly in a continuous regimen, or daily for 3 weeks of a 4-week cycle. In women with an intact uterus, the endometrial safety of topical oestrogen therapy is uncertain. The addition of a progestogen should be considered, although it might not be required during low-dose, short-term topical oestrogen treatment. During long-term therapy, these women should be monitored for evidence of endometrial hyperplasia, whether or not a progestogen is also used.

When given as replacement therapy on a cyclical basis, oral doses of 1.25 mg daily are used for primary ovarian failure, adjusted according to response. Doses of 300 to 625 micrograms daily are usually given for female hypogonadism, although higher doses were formerly used.

For the palliative treatment of prostatic carcinoma (p. 712.3), an oral dose of 1.25 to 2.5 mg three times daily has been used. A dose of 10 mg three times daily for at least 3 months has been used for palliative treatment of breast carcinoma in men (p. 704.1) and postmenopausal women (p. 702.1).

Abnormal uterine bleeding has been treated acutely by giving 25 mg of conjugated oestrogens by slow intravenous injection, repeated if required after 6 to 12 hours; the intramuscular route has also been used.

Synthetic conjugated oestrogens are derived from plant material, and are not a generic equivalent of Conjugated Estrogens described in USP 36 (see above). Synthetic conjugated estrogens, A, contains a mixture of nine derivatives of estrone, equilin, estradiol, and equilenin. It is used in oral doses of 0.45 to 1.25 mg daily for the relief of vasomotor symptoms associated with the menopause. An oral dose of 300 micrograms daily may be used for menopausal vulvar and vaginal atrophy, but an alternative, topical therapy should be considered if this is the only symptom being treated. For local management of moderate to severe vaginal dryness or dyspareunia associated with menopausal vulvar and vaginal atrophy, 1 g of a 0.0625% vaginal cream may be used daily for 1 week followed by 1 g twice weekly. As for vaginal conjugated oestrogens, above, the addition of a progestogen should be considered for women with a uterus. Synthetic conjugated estrogens, B, contains a mixture of ten derivatives of estrone, equilin, estradiol, and equilenin. It is used in oral doses of 0.3 to 1.25 mg daily for the relief of vasomotor symptoms associated with the menopause. An oral dose of 300 micrograms daily may be used for relief of symptoms associated with menopausal vulvar and vaginal atrophy, but an alternative, topical therapy should be considered if this is the only symptom being treated.

Administration in children. Conjugated oestrogens have been used to reduce final height in girls with constitutional tall stature (see Growth Disorders, under Estradiol, p. 2272.2). They have also been used in children for some haemorrhagic disorders (below).

Haemorrhagic disorders. Case reports and small studies have described the use of high-dose conjugated oestrogens in the management of haemorrhagic disorders associated with renal failure,[1-5] although it is unclear how oestrogens might reduce prolonged bleeding times in these patients.[6] Treatment has been given orally, but an intravenous dose of 600 micrograms/kg given over 30 to 40 minutes, once daily for 5 days, has been reported most often.[6]

Conjugated oestrogens have also been used in various doses in the management of haemorrhagic cystitis (p. 2347.3), particularly that caused by high-dose cyclophosphamide therapy (p. 772.3). The successful use of 25 mg intravenously for 2 consecutive days has been reported,[7] as has a regimen consisting of a 1 mg/kg intravenous dose followed by 5 mg orally for 3 weeks.[8] A report[9] of treatment in 10 patients described the use of oral conjugated oestrogens in doses of 6 to 12 mg daily, usually in three divided doses, for durations of 5 days to 16 weeks.[9] Another report[10] of therapy in 10 children aged between 8 and 19 years described intravenous doses of 12.5 to 50 mg twice daily, often for 2 or 3 days, followed by oral doses ranging from 2.5 mg twice daily to 5 mg four times daily for durations of a few days to about 3 weeks.

Oestrogens have also been used in the treatment of other bleeding disorders (see Estradiol, p. 2272.2).

1. Liu YK, *et al.* Treatment of uraemic bleeding with conjugated oestrogen. *Lancet* 1984; ii: 887–90.
2. Livio M, *et al.* Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 1986; 315: 731–5.
3. Seth S, Geier TM. Use of conjugated estrogens to control gastrointestinal tract bleeding in two patients with chronic renal failure. *Clin Pharm* 1988; 7: 906–9.
4. Shemin D, *et al.* Oral estrogens decrease bleeding time and improve clinical bleeding in patients with renal failure. *Am J Med* 1990; 89: 436–40.
5. Heunisch C, *et al.* Conjugated estrogens for the management of gastrointestinal bleeding secondary to uremia of acute renal failure. *Pharmacotherapy* 1998; 18: 210–7.
6. Hedges SJ, *et al.* Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007; 3: 138–53.
7. Kopterides P, *et al.* Cyclophosphamide-induced hemorrhagic cystitis successfully treated with conjugated estrogens. *Am J Hematol* 2005; 80: 166–7.
8. Rodriguez Luna JM, *et al.* Control of massive hematuria in idiopathic hemorrhagic cystitis after administration of conjugated estrogen. *J Urol (Baltimore)* 1992; 148: 1524–5.
9. Ordemann R, *et al.* Encouraging results in the treatment of haemorrhagic cystitis with estrogen--report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; 25: 981–5.
10. Heath JA, *et al.* Estrogen as treatment of hemorrhagic cystitis in children and adolescents undergoing bone marrow transplantation. *Bone Marrow Transplant* 2006; 37: 523–6.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). See also under Hormone Replacement Therapy, p. 2246.3 and p. 2250.1.

Effects on the cardiovascular system. In an early study of *men* with a previous myocardial infarction, treatment with conjugated oestrogens 5 mg daily was stopped because of a higher incidence of subsequent coronary events.[1] Moreover, treatment with the lower 2.5 mg dose was later also stopped because of suggestions of adverse trends including a greater incidence of venous thromboembolism.[2]

For the cardiovascular effects of HRT, including conjugated oestrogens, in women, see p. 2248.2.

1. Coronary Drug Project Research Group. The Coronary Drug Project: initial findings leading to modifications of its research protocol. *JAMA* 1970; 214: 1303–13.
2. Coronary Drug Project Research Group. The Coronary Drug Project: findings leading to discontinuation of the 2.5-mg/day estrogen group. *JAMA* 1973; 226: 652–7.

Effects on the nervous system. Reversible chorea has been described in 2 women given conjugated oestrogens with a progestogen as postmenopausal HRT;[1,2] in 1 case the patient had a history of migraine and Sydenham's chorea.[1] Chorea also recurred in a postmenopausal woman with a history of chorea gravidarum when she was given vaginal conjugated oestrogens.[3]

1. Steiger MJ, Quinn NP. Hormone replacement therapy induced chorea. *BMJ* 1991; 302: 762.
2. Suchowersky O, Muthipeedika J. A case of late-onset chorea. *Nat Clin Pract Neurol* 2005; 1: 113–16.
3. Caviness JN, Muenter MD. An unusual cause of recurrent chorea. *Mov Disord* 1991; 6: 355–7.

Hypersensitivity. An anaphylactic reaction after intravenous conjugated oestrogens has been reported.[1]

1. Searcy CJ, *et al.* Anaphylactic reaction to intravenous conjugated estrogens. *Clin Pharm* 1987; 6: 74–6.

Interactions

See under Hormone Replacement Therapy, p. 2251.1.

Pharmacokinetics

Conjugated oestrogens taken orally are hydrolysed by enzymes present in the intestine that remove the sulfate group and allow absorption of the unconjugated oestrogen.

Metabolism occurs mainly in the liver; there is some enterohepatic recycling (see also under Estradiol, p. 2273.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Belestar; Livomarin; Premarin; *Austral.*: Premarin; *Braz.*: Estrinolon; Estrogenon; Estroplus; Gestrocon; Menoprin; Prem; Premarin; Repogen; *Canad.*: Apo-Conest†; CES; Congest; Premarin; *Chile*: Climatrol E; Conpremin; Estrarona; Profemina†; *China*: Premarin (倍美力); *Ger.*: Climopax mono; Presomen; *Gr.*: Premarin; *Hong Kong*: Equin; Premarin; *India*: Espauz; Estrin; Premarin; *Irl.*: Premarin; *Israel*: Estrogenus; *Malaysia*: Premarin; *Mex.*: DNA-EC; Equifan; Esonovag; Fahifem; Neradin; Premarin; Six Din; Sultrona; Terapova; *Neth.*: Dagynil; *NZ*: Premarin; *Philipp.*: Menpoz†; Premarin; Primax; *S.Afr.*: Premarin; *Singapore*: Equin; Premarin; *Spain*: Equin†; *Thal.*: Estromon; Premarin; *Turk.*: Premarin; *UK*: Premarin; *USA*: Genestin; Enjuvia; Premarin; *Venez.*: Biostrogen; Climatrol E; Menostat; Premarin.

Multi-ingredient Preparations. *Austral.*: Premia Continuous; Premia†; *Braz.*: Menotensil; Premelle Ciclo; Premelle; Prempro Bifasico; Prempro Monofasico; Repogen Ciclo; Repogen Cont; Selecta; *Canad.*: Premplus; *Chile*: Climatrol Continuo†; Climatrol HT Continuo; Climatrol HT†; Conpremin Pak Plus†; Conpremin Pak†; Novafac 30; Novafac CC; Novafac†; Profemina MP†; *China*: Premelle (倍美罗); *Ger.*: Climopax Cyclo; Climopax; Presomen Compositum; Presomen cont; *Gr.*: Premelle Cycle; Premelle; *Hong Kong*: Premelle Cycle†; Premelle; *India*: Conjugase; *Irl.*: Premique Cycle; Premique; Prempak-C; *Ital.*: Premelle Combinato†; Premia; *Malaysia*: Premelle; *Mex.*: Premelle; *NZ*: Premia Continuous; *Philipp.*: Premelle Cycle; Premelle; *S.Afr.*: Premelle Cycle; Premelle; Prempak N†; *Singapore*: Premelle Cycle; Premelle; Prempak-C†; *Turk.*: Premelle Cycle; Premelle†; *UK*: Premique Cycle†; Premique; Prempak-C; *USA*: Duavee; Premphase; Prempro; *Venez.*: Climatrol HT Ciclico; Climatrol HT Continuo; Premelle Continuo.

Pharmacopoeial Preparations
USP 36: Conjugated Estrogens Tablets.

Corifollitropin Alfa *(BAN, USAN, rINN)*

Corifollitropina alfa; Corifollitropine Alfa; Corifollitropinum Alfa; FSH-CTP; Org-36286; Корифоллитропин Альфа.

Follicle-stimulating hormone (human α-subunit reduced), complex with follicle-stimulating hormone (human β-subunit reduced), fusion protein with 118-145-chorionic gonadotropin (human β-subunit).

CAS — 995962-73-3.
ATC — G03GA09.
ATC Vet — QG03GA09.
UNII — 77KG9Y2GWX.

Uses and Administration

Corifollitropin alfa is a recombinant DNA product that has a prolonged duration of follicle-stimulating activity. It is used with a gonadorelin (gonadotrophin releasing hormone) antagonist for controlled ovarian stimulation, to be used in assisted reproduction techniques in women with anovulatory infertility (see Infertility, p. 2253.1).

Treatment should be started during the early follicular phase of the menstrual cycle.

- On day 1 of a treatment cycle corifollitropin alfa is given as a single subcutaneous injection into the abdominal wall. A dose of 100 micrograms is used for women weighing 60 kg or lighter and 150 micrograms for those heavier than 60 kg.
- Treatment with a gonadorelin antagonist may then be given on day 5 or 6 depending on ovarian response.
- On day 8, usual daily injections of 150 units of a recombinant follicle-stimulating hormone may be started. Adequate follicular development is usually achieved by the ninth day (range 6 to 18 days).
- When adequate follicular development is seen, a single injection of 5000 to 10 000 units of chorionic gonadotrophin is given on the same or next day to induce ovulation.

References.
1. Devroey P, *et al.* Induction of multiple follicular development by a single dose of long-acting recombinant follicle-stimulating hormone (FSH-CTP, corifollitropin alfa) for controlled ovarian stimulation before in vitro fertilization. *J Clin Endocrinol Metab* 2004; 89: 2062–70.
2. Balen AH, *et al.* Pharmacodynamics of a single low dose of long-acting recombinant follicle-stimulating hormone (FSH-carboxy terminal peptide, corifollitropin alfa) in women with World Health Organization group II anovulatory infertility. *J Clin Endocrinol Metab* 2004; 89: 6297–6304.
3. Corifollitropin Alfa Dose-finding Study Group. A randomized dose-response trial of a single injection of corifollitropin alfa to sustain multifollicular growth during controlled ovarian stimulation. *Hum Reprod* 2008; 23: 2484–92.
4. Fauser BCJM, *et al.* Advances in recombinant DNA technology: corifollitropin alfa, a hybrid molecule with sustained follicle-stimulating activity and reduced injection frequency. *Hum Reprod Update* 2009; 15: 309–21.
5. Devroey P, *et al.* ENGAGE Investigators. A double-blind, non-inferiority RCT comparing corifollitropin alfa and recombinant FSH during the first seven days of ovarian stimulation using a GnRH antagonist protocol. *Hum Reprod* 2009; 24: 3063–72.

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p. 2284.3.

Ovarian response may be greater after corifollitropin alfa than after follicle-stimulating hormone and careful monotoring for signs of ovarian hyperstimulation syndrome is recommended for patients receiving their first cycle of treatment. Use in women with impaired renal function is not recommended.

Pharmacokinetics

Corifollitropin alfa is absorbed after subcutaneous injection with an absolute bioavailability of 58% and peak serum concentrations occur after 44 hours. It is eliminated mainly through the kidneys and has an elimination half-life of 69 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Elonva; *Austria*: Elonva; *Belg.*: Elonva; *Cz.*: Elonva; *Denm.*: Elonva; *Ger.*: Elonva; *Gr.*: Elonva; *Israel*: Elonva; *Neth.*: Elonva; *Norw.*: Elonva; *Pol.*: Elonva; *Port.*: Elonva; *Singapore*: Elonva; *Spain*: Elonva; *Swed.*: Elonva; *UK*: Elonva.

Cyclofenil *(BAN, rINN)* ⊗

Ciclofenilo; Cyclofenil; Cyclofenilum; Cyklofenil; F-6066; H-3452; ICI-48213; Siklofenil; Syklofeniili; Циклофенил.

4,4′-(Cyclohexylidenemethylene)bis(phenyl acetate).
$C_{23}H_{24}O_4$=364.4
CAS — 2624-43-3.
ATC — G03GB01.
ATC Vet — QG03GB01.
UNII — J468V64WZ1.

Profile

Cyclofenil is a nonsteroidal anti-oestrogen that has been used in the treatment of menstrual disturbances and anovulatory infertility due to hypothalamic-pituitary dysfunction.

It has been given orally in doses of 200 mg three times daily for 5 days, in a cyclical regimen for 3 or 4 cycles. It has also been given for menopausal symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Menopax; *Ital.*: Neodym; *Turk.*: Fertodur†.

Cyproterone Acetate *(BANM, USAN, rINNM)*

Acetato de ciproterona; Ciproterona, acetato de; Ciproteron-acetat; Ciproterono acetatas; Cyproteronacetat; Cyproteron-acetát; Cyprotérone, Acétate de; Cyproteroni Acetas; NSC-81430; SH-714; SH-881 (cyproterone); Siproteron Asetat; Syproteroniasetaatti; Ципротерона Ацетат.

6-Chloro-1β,2β-dihydro-17α-hydroxy-3′*H*-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione acetate.
$C_{24}H_{29}ClO_4$=416.9
CAS — 2098-66-0 (cyproterone); 427-51-0 (cyproterone acetate).
ATC — G03HA01.
ATC Vet — QG03HA01.
UNII — 4KM2BNSJHF.

NOTE. Compounded preparations of cyproterone acetate may be represented by the following names:

- Co-cyprindiol (*BAN*)—cyproterone acetate 2000 parts and ethinylestradiol 35 parts (w/w).

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

Ph. Eur. 8: (Cyproterone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone; very soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Uses and Administration

Cyproterone acetate is a progestogen (see Progesterone, p. 2300.2) with anti-androgenic properties.

It is used for the **control of libido** in severe hypersexuality or sexual deviation in men (see Disturbed Behaviour, p. 1030.2). The usual oral dose is 50 mg twice daily after meals. Given by depot intramuscular injection, a dose of 300 mg once every 10 to 14 days has been used to control libido. When a satisfactory effect has been obtained, the dose may be reduced by gradually increasing the interval between injections until a stable maintenance dose is reached.

It is also used for the palliative treatment of **prostatic carcinoma** (p. 712.3), to control the initial disease flare associated with gonadorelin analogue therapy, and to control hot flushes associated with gonadorelin analogues or orchidectomy. In palliative treatment where gonadorelin analogues or surgery are contra-indicated, not tolerated, or where oral therapy is preferred, oral doses of 200 to 300 mg daily are given in 2 or 3 divided doses after meals. For the suppression of disease flare, cyproterone acetate is given orally in a dose of 100 mg twice daily; it is used alone for 5 to 7 days, then with the gonadorelin analogue for 3 to 4 weeks. For the treatment of hot flushes, an oral dose of 50 mg daily is used; this may be increased up to 150 mg daily in 3 divided doses if necessary. In palliative therapy of prostatic carcinoma, 300 mg may be given intramuscularly once every 2 weeks after orchidectomy, or once weekly without orchidectomy.

Cyproterone acetate may be used with ethinylestradiol in women for the control of moderate to severe androgen-dependent **acne**, when topical treatment or systemic antibacterials have failed, and in **hirsutism**. The usual oral doses are 2 mg of cyproterone acetate with 35 micrograms of ethinylestradiol given daily for 21 days of each menstrual cycle; the first treatment course is started on the first day of the menstrual cycle and each subsequent course is started after 7 tablet-free days have followed the preceding course. This regimen also provides contraception, and patients relying on this effect should be given the same advice regarding missed doses and reduced efficacy due to vomiting and diarrhoea as that given for combined oral contraceptives (see p. 2231.3); additional hormonal contraception is not necessary and should not be used. At least 3 months of treatment is generally needed, and the need for continuing therapy should be regularly assessed. Regimens using higher doses may be given in more severe cases of hyperandrogenism. Doses of 50 or 100 mg daily for the first 10 days of the menstrual cycle may be used, with a combined hormonal contraceptive given to stabilise the cycle and avoid pregnancy. The dose should be reduced once there has been a satisfactory response. For other high-dose regimens that have been used, see Acne, below, and Hirsutism, p. 2262.1.

Dose-related hepatotoxicity has occurred with cyproterone, particularly in men treated for prostate cancer (see Effects on the Liver, p. 2262.3, and Precautions, p. 2263.1).

For the use of cyproterone acetate for precocious puberty in children, see p. 2262.2.

Administration in children. Cyproterone acetate may be used in the management of precocious puberty (see p. 2262.2).

Acne. Cyproterone acetate may be used in the management of acne (p. 1682.2) in women with signs of hyperandrogenism. An oral combination of cyproterone acetate 2 mg with ethinylestradiol 35 micrograms, which also provides contraception, is used when the condition is moderate to severe. A systematic review[1] considered that combinations such as this were more effective in the treatment of acne than combined oral contraceptives containing levonorgestrel, but noted that this was based on limited evidence. In more severe disease, higher doses of cyproterone have been added to this low-dose regimen; examples include giving cyproterone acetate 50 mg daily for 10 or 21 days of each cycle.[2]

1. Arowojolu AO, *et al.* Combined oral contraceptive pills for treatment of acne. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2012 (accessed 19/12/13).
2. Beylot C, *et al.* Oral contraceptives and cyproterone acetate in female acne treatment. *Dermatology* 1998; 196: 148–52.

Alopecia. Cyproterone acetate has been tried in the treatment of female-pattern alopecia (p. 1682.3). In premenopausal women, oral doses of 50 or 100 mg daily have usually been given in sequential regimens with an oestrogen or combined oral contraceptive; continuous treatment using 50 mg daily has been given to postmenopausal women. It has generally been considered that women with other signs of hyperandrogenism, such as acne and seborrhoea, as well as hair loss are most likely to benefit from cyproterone but results from small studies have been mixed.[1-3]

1. Vexiau P, *et al.* Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol* 2002; 146: 992–9.
2. Carmina E, Lobo RA. Treatment of hyperandrogenic alopecia in women. *Fertil Steril* 2003; 79: 91–5.
3. Sinclair R, *et al.* Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol* 2005; 152: 466–73.

Gender reassignment. Cyproterone acetate is used for its anti-androgenic effects in male-to-female transsexuals.[1,2]

An oral dose of 50 mg twice daily is usually given with an oestrogen (see Estradiol, p. 2272.2).

1. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; 64 (suppl 2): 31–6.
2. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; 93: 19–25.

Hidradenitis suppurativa. Beneficial responses to cyproterone acetate with ethinylestradiol have been seen[1-3] in women with hidradenitis suppurativa, an androgen-dependent disorder of the skin and hair in the pubic and axillary regions.

1. Mortimer PS, *et al.* A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol* 1986; 115: 263–8.
2. Sawers RS, *et al.* Control of hidradenitis suppurativa in women using combined antiandrogen (cyproterone acetate) and oestrogen therapy. *Br J Dermatol* 1986; 115: 269–74.
3. Mortimer PS, *et al.* Mediation of hidradenitis suppurativa by androgens. *BMJ* 1986; 292: 961.

Hirsutism. Hirsutism is an abnormal growth in females of coarse pigmented terminal hair in an adult male pattern, and is one of the clinical expressions of hyperandrogenism. Most women with hirsutism have increased concentrations of circulating androgens from the ovaries associated with polycystic ovary syndrome (p. 2253.3). However, many women with mild hirsutism have idiopathic hirsutism; they have regular menses and normal serum-androgen concentrations but the hair follicles are more sensitive to the effects of androgens. In rare cases, the adrenal gland is the primary source of increased androgens, for example, in congenital adrenal hyperplasia (p. 1603.2). In a few cases, severe hirsutism is associated with frank virilisation due to massively increased circulating androgen concentrations from an androgen-secreting tumour. Hirsutism is an adverse effect of androgenic progestogens, such as norgestrel, used in hormonal contraceptives and HRT. Androgens and anabolic steroids may also cause hirsutism in females.

Treatment for hirsutism includes cosmetic treatments such as bleaching, shaving, plucking, electrolysis, and laser hair removal, and in the mildest cases this may be all that is required. However, such mechanical means of treatment are more usually combined with drug therapy to prevent further conversion of vellus to terminal hair, and to slow the regrowth of terminal hair, which may become lighter and softer. Because the growth cycle of hair is long, a response to therapy may not be seen for 6 to 12 months.[1-4]

Combined *hormonal contraceptives* containing non-androgenic progestogens are widely used for hirsutism but their effects are generally limited.[1-3] *Drospirenone*, a progestogen used in combined oral contraceptives, has a very weak anti-androgenic effect.[4] The mainstay of oral drug therapy for hirsutism is an anti-androgen, the most commonly used being the steroidal anti-androgens *cyproterone acetate* and *spironolactone*. To increase efficacy (by suppressing ovarian androgen production) and minimise the chance of conception (because of the risk of feminisation of a male fetus), cyclical ethinylestradiol is commonly used with cyproterone acetate. Combined non-androgenic hormonal contraceptives are commonly used with spironolactone, which has no progestogenic activity. Cyproterone acetate may be used in a low-dose combined preparation containing cyproterone acetate 2 mg with ethinylestradiol 35 micrograms.[2-5] In more severe hirsutism, the two drugs may be prescribed separately in a 'reversed sequential regimen'. High-dose regimens[2] have used cyproterone acetate 100 mg daily given on days 5 to 14 of the menstrual cycle with ethinylestradiol 50 micrograms on days 5 to 24. However, lower doses are also effective, with fewer adverse effects; such regimens include[5] cyproterone acetate 50 mg (days 5 to 15) with ethinylestradiol 20 micrograms (days 5 to 25), or cyproterone acetate 12.5 mg (days 5 to 15) with ethinylestradiol 10 to 20 micrograms (days 5 to 25). Alternatively,[2] cyproterone acetate 25 to 50 mg daily may be added to the first 10 days of any low-dose combined oral contraceptive. When a satisfactory response has been achieved, the cyproterone dosage is gradually reduced, and eventually the low-dose combination preparation may be sufficient. In some countries spironolactone is the drug of choice for the treatment of hirsutism, particularly if there is associated obesity and hypertension; doses of 100 to 200 mg daily are generally used.[1,2,5] Despite its wide use, however, evidence of benefit is considered scanty.[6]

Flutamide, *finasteride*, and *leuprorelin* have also been shown to be effective, although some consider finasteride to be less active.[5] These are not recommended for routine management of hirsutism;[4] flutamide can cause hepatotoxicity, and long-term use of gonadorelin analogues reduces bone mineral density. Finasteride has significant teratogenic potential.[2] The condition has also been reported to respond to *ketoconazole*. *Eflornithine* is used topically for the reduction of facial hair.[1,3,5] It is thought to slow hair growth by the inhibition of ornithine decarboxylase in hair follicles. Eflornithine may be used alone or with other therapies, including laser hair removal.[4]

Corticosteroids can suppress adrenal androgen production, but results with *dexamethasone* have been disappointing and the addition of an anti-androgen is usually needed.[5] Corticosteroids may have a limited role in managing hirsutism associated with nonclassic congenital adrenal hyperplasia.[1,4]

1. Rosenfield RL. Hirsutism. *N Engl J Med* 2005; 353: 2578–88.
2. Claman P, *et al.*, Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guidelines no. 110, January 2002: Hirsutism: evaluation and treatment. *J Obstet Gynaecol Can* 2002; 24: 62–7. Also available at: .. http://www.sogc.org/guidelines/public/110E-CPG-January2002.pdf (accessed 27/06/08)
3. Moghetti P, Toscano V. Treatment of hirsutism and acne in hyperandrogenism. *Best Pract Res Clin Endocrinol Metab* 2006; 20: 221–34.
4. Martin KA, *et al.* Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008; 93: 1105–20. Also available at: http://www.endo-society.org/guidelines/final/upload/Hirsutism_Guideline.pdf (accessed 20/11/09)
5. Carmina E. A risk-benefit assessment of pharmacological therapies for hirsutism. *Drug Safety* 2001; 24: 267–76.
6. 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 20/11/09).

Precocious puberty. Although cyproterone acetate has been used for the treatment of central precocious puberty (p. 2254.1), it has generally been superseded and is now given in a short course to prevent the initial stimulatory effect of gonadorelin analogue therapy. The use of an oral dose of cyproterone acetate 50 mg twice daily, given from 3 weeks before to 2 weeks after starting the gonadorelin analogue, has been reported.[1] Menstrual-like bleeding may occur in girls after stopping cyproterone, depending on the degree of precocity. Gonadorelin analogue therapy does not control adrenal production of sex hormones, which, if overactive, can stimulate adrenarche and advancement of bone age; cyproterone acetate in usual doses of 10 to 20 mg twice daily has been used to treat this.[1]

Cyproterone acetate may sometimes be used to suppress sexual maturation in the management of peripheral forms of precocious puberty. Although it is not licensed for this, the *BNFC* includes an initial oral dose of 25 mg twice daily, adjusted according to response.

1. Laron Z, Kauli R. Experience with cyproterone acetate in the treatment of precocious puberty. *J Pediatr Endocrinol Metab* 2000; 13 (suppl): 805–10.

Adverse Effects

When given to men cyproterone reduces libido, inhibits spermatogenesis, reduces the volume of ejaculate, and causes infertility. There may be azoospermia after 8 weeks and slight atrophy of the seminiferous tubules, but these changes are slowly reversible and spermatogenesis usually recovers to pre-treatment levels about 3 to 5 months after stopping cyproterone. Abnormal spermatozoa may be produced. Gynaecomastia is common and permanent enlargement of the mammary glands may occur; galactorrhoea and benign nodules have been reported rarely. Fatigue and weakness are common and depressive mood changes can occur occasionally. Patients may have weight changes, alterations in hair pattern, dry skin, and rarely rashes or hypersensitivity. Shortness of breath may occur, and anaemia and osteoporosis have been reported rarely. Liver function tests may be altered; there have also been reports of hepatitis, jaundice, and hepatic failure, sometimes fatal, developing usually after several months of high-dose cyproterone therapy, but an association with liver cancer is uncertain. High doses of cyproterone have also been associated with reports of meningioma.

When low-dose cyproterone is given with ethinylestradiol to women, adverse effects associated with combined oral contraceptives (see p. 2233.3) may occur.

Carcinogenicity. See Effects on the Brain and Effects on the Liver, below.

Effects on the brain. Meningiomas, including multiple meningiomas, have been reported in patients given high doses of cyproterone acetate. Up to September 2009, the MHRA was aware of 36 cases worldwide, 19 of which were multiple meningiomas. Women accounted for 32 cases, and most were in France where there is extensive use of high-dose cyproterone for the treatment of hyperandrogenism. The dose was higher than 25 mg daily in all but 1 case, and the duration of treatment had ranged from 4 to 27 years.[1] The MHRA advised that patients with existing meningioma, or a history of meningioma, must not be given high doses of cyproterone acetate (25 mg or more daily). However, this advice did not apply to low-dose products, such as those containing co-cyprindiol (2 mg daily of cyproterone acetate orally with ethinylestradiol).

1. MHRA/CHM. High-dose cyproterone acetate: potential risk of (multiple) meningiomas. *Drug Safety Update* 2009; 3 (3): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON059813&RevisionSelectionMethod=LatestReleased (accessed 13/11/09)

Effects on the cardiovascular system. Combined oral contraceptives are associated with a small increased risk of cardiovascular disease (see p. 2237.1), which also applies to the combination of cyproterone acetate and an oestrogen. In 2002, the UK CSM[1] warned that preparations containing cyproterone and ethinylestradiol should not be used solely for contraception, but for treatment of severe acne that had not responded to oral antibacterials, or for moderately severe hirsutism, and that they should be withdrawn 3 or 4 cycles after the treated condition has completely resolved. However, others[2,3] questioned some study results, concluding that preparations containing cyproterone were not associated with a risk in excess of that associated with conventional combined oral contraceptives including those containing levonorgestrel. Some[4] also called for the removal of the CSM recommendation to limit the duration of therapy, particularly as acne and hirsutism frequently recur after stopping cyproterone therapy. In 2008, the CHM (formerly the CSM) reconfirmed its 2002 advice on the use of cyproterone with ethinylestradiol.[5] However, it added that for women with severe hyperandrogenism, in whom symptoms usually recur when treatment is stopped, therapy could be continued with regular specialist review until the symptoms were judged unlikely to recur. It was also recommended that, for all women, treatment can be restarted at any time if acne or hirsutism recurs after stopping therapy.

In 2013, the EMA concluded from an updated review of data that the risk of venous thromboembolism associated with co-cyprindiol (cyproterone acetate 2 mg with ethinylestradiol 35 micrograms) was 1.5 to 2 times higher than for combined oral contraceptives containing levonorgestrel, and may be similar to that associated with contraceptives containing desogestrel, drospirenone, or gestodene. However, it suggested that the balance of benefits and risks of co-cyprindiol remained positive in moderate to severe androgen-sensitive acne and hirsutism, and reminded prescribers that it should not be used solely for contraception or with an additional hormonal contraceptive.[6]

The study of any association may be confounded by the adverse cardiovascular risk associated with polycystic ovary disease, an underlying condition in many women given cyproterone with ethinylestradiol to manage acne and hirsutism.[3]

1. CSM/MCA. Cyproterone acetate (Dianette): risk of venous thromboembolism (VTE). *Current Problems* 2002; 28: 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 27/06/08)
2. Spitzer WO. Cyproterone acetate with ethinylestradiol as a risk factor for venous thromboembolism: an epidemiological evaluation. *J Obstet Gynaecol Can* 2003; 25: 1011–18.
3. Seaman HE, *et al.* Venous thromboembolism associated with cyproterone acetate in combination with ethinyloestradiol (Dianette): observational studies using the UK General Practice Research Database. *Pharmacoepidemiol Drug Safety* 2004; 13: 427–36.
4. Franks S, *et al.* Cyproterone acetate/ethinyl estradiol for acne and hirsutism: time to revise prescribing policy. *Hum Reprod* 2008; 23: 231–2.
5. MHRA/CHM. Cyproterone acetate with ethinylestradiol (co-cyprindiol): recommended duration of use. *Drug Safety Update* 2008; 1 (9): 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON045066&RevisionSelectionMethod=LatestReleased (accessed 22/08/08)
6. EMA. Benefits of Diane 35 and its generics outweight risks in certain patient groups (issued 25th July, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/cyproterone_ethinylestradiol_107i/European_Commission_final_decision/WC500147176.pdf (accessed 11/12/13)

Effects on the eyes. Bilateral optic atrophy in an elderly male patient was thought to be associated with cyproterone.[1] The authors could find no other cases from the published literature or the manufacturers' records. Central retinal vein occlusion occurred in a 28-year-old woman given cyproterone for the treatment of hair loss.[2]

1. Markus H, *et al.* Visual loss and optic atrophy associated with cyproterone acetate. *BMJ* 1992; 305: 159.
2. Zaoui M, *et al.* Occlusion de la veine centrale de la rétine sous anti-androgènes. *J Fr Ophtalmol* 2000; 23: 42–4.

Effects on the liver. There have been many reports of hepatic reactions associated with cyproterone acetate. In February 1995, the UK CSM noted that it had received 96 reports (33 fatal) of reactions including hepatitis, cholestatic jaundice, and hepatic failure, after cyproterone treatment;[1] 91 of these were in elderly men typically given high doses (300 mg daily) for prostatic cancer, and toxicity usually developed after several months of treatment. In view of this it was recommended that the use of cyproterone acetate in prostatic cancer be restricted to short courses for the testosterone flare associated with the commencement of gonadorelin analogue therapy, or for hot flushes after surgical or chemical castration, or for patients unresponsive to, or intolerant of, other treatments. A retrospective analysis[2] of data from 105 patients with advanced prostate cancer, who had received cyproterone

acetate 150 mg daily, found mild to moderate hepatotoxicity in 6 patients and severe toxicity in 4. There was a higher occurrence of hepatotoxicity (19 cases out of 124 patients) in a similar group that had been given flutamide. Fourteen published case reports have also been briefly reviewed.[3] Patients with chronic viral hepatitis might be at higher risk of developing hepatotoxicity from cyproterone therapy.[4]

Although there is little doubt of the risk of hepatotoxicity, suggestions of an association between cyproterone therapy and the development of liver cancer remain contentious. There are individual reports of hepatocellular carcinoma developing in patients receiving cyproterone,[5,6] and some evidence *in vitro* of the formation of DNA adducts in exposed hepatocytes,[7] but there does not seem to be clinical evidence to support any association between use of cyproterone acetate and the development of liver tumours.[7,8]

1. CSM/MCA. Hepatic reactions with cyproterone acetate (Cyprostat, Androcur). *Current Problems* 1995; 21: 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 27/06/08)
2. Lin ADY, *et al.* Antiandrogen-associated hepatotoxicity in the management of advanced prostate cancer. *J Chin Med Assoc* 2003; 66: 735–40.
3. Savidou I, *et al.* Hepatotoxicity induced by cyproterone acetate: a report of three cases. *World J Gastroenterol* 2006; 12: 7551–5.
4. Pu Y-S, *et al.* Antiandrogen hepatotoxicity in patients with chronic viral hepatitis. *Eur Urol* 1999; 36: 293–7.
5. Watanabe S, *et al.* Three cases of hepatocellular carcinoma among cyproterone users. *Lancet* 1994; 344: 1567–8.
6. Rüdiger T, *et al.* Hepatocellular carcinoma after treatment with cyproterone acetate combined with ethinylestradiol. *Lancet* 1995; 345: 452–3.
7. Lewis S. Warning on cyproterone. *Lancet* 1995; 345: 347.
8. Rabe T, *et al.* Liver tumours in women on oral contraceptives. *Lancet* 1994; 344: 1568–9.

Precautions

When used for hypersexuality, cyproterone is *contra-indicated in men with liver diseases or malignant or wasting diseases.* In addition, it should not be given to patients with severe chronic depression, severe diabetes with vascular changes, or sickle-cell anaemia. It should also be avoided in those with existing, or a history of, thromboembolic disorders or meningioma (see also Effects on the Brain, p. 2262.2). It may delay bone maturation and testicular development and so should not be given to immature youths. When used for prostate cancer, there are no absolute contra-indications to the use of cyproterone (except perhaps meningioma), but the above conditions should prompt cautious consideration of the risks and benefits.

In men treated with cyproterone, liver function should be monitored before starting, and regularly during treatment, and whenever any symptoms or signs suggestive of hepatotoxicity occur. If cyproterone-induced hepatotoxicity occurs, treatment should be withdrawn. In men with prostate cancer, it may be advisable to limit the duration of treatment (see Effects on the Liver, p. 2262.3). Men with diabetes require careful monitoring of diabetic control. Since anaemia has been seen, regular blood counts are recommended before and during treatment. Adrenocortical suppression has been reported and function should be monitored regularly during treatment. Patients should be advised that fatigue and weakness are common and may interfere with driving and the operation of machinery.

Similar precautions apply to women treated with high doses of cyproterone for hyperandrogenism. When low doses are used with ethinylestradiol (co-cyprindiol), the precautions for combined oral contraceptives (see p. 2240.3) should be observed.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyproterone 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 04/10/11)

Pregnancy. Use of cyproterone during pregnancy might carry a risk of feminisation of a male fetus. However, there are a few case reports of healthy male infants born to mothers who had inadvertently taken a combination of cyproterone acetate and ethinylestradiol during the early stages of pregnancy,[1,2] and of a male fetus that was found to have no malformations after abortion was induced.[3] For further information on oral contraceptive use in pregnancy, see p. 2242.1.

1. Statham BN, *et al.* Conception during 'Diane' therapy—a successful outcome. *Br J Dermatol* 1985; 113: 374.
2. Bye P. Comments on 'conception during "Diane" therapy—a successful outcome'. *Br J Dermatol* 1986; 114: 516.
3. Bergh T, Bakos O. Exposure to antiandrogen during pregnancy: case report. *BMJ* 1987; 294: 677–8.

Interactions

UK licensed product information states that alcohol may reduce the efficacy of cyproterone acetate as it is ineffective in chronic alcoholics. Dosage requirements of oral antidiabetics and insulin may be altered because of cyproterone's effects on carbohydrate metabolism.

When given with ethinylestradiol to women, interactions similar to those for combined oral contraceptives (see p. 2242.3) might be anticipated.

Pharmacokinetics

Cyproterone acetate is slowly absorbed from the gastrointestinal tract; peak plasma concentrations occur in about 3 hours. It is about 96% bound to plasma proteins, mainly albumin. The terminal elimination half-life is about 43 hours. Cyproterone is metabolised by various pathways including hydroxylation and conjugation; about 35% of a dose is excreted in urine, the remainder being excreted in the bile. The principal metabolite, 15β-hydroxycyproterone, has anti-androgenic activity.

The elderly. In a study[1] of healthy men, a decrease in hepatic clearance of cyproterone acetate was found in elderly men and thought to be due to an age-related reduction in liver volume.

1. Kuhnz W, *et al.* Investigation into the age-dependence of the pharmacokinetics of cyproterone acetate in healthy male volunteers. *Eur J Clin Pharmacol* 1997; 53: 75–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Androcur; Androstat; Asoteron; Ceprater; Ciclamil; Ciprofarma; Ciproplex; Kebirterona; Omnigeriat; Purflix; *Austral.*: Androcur; Cyprohexal; Cyprone; Cyprostat; Procur; *Austria*: Andro-Diane; Androcur; *Belg.*: Androcur; Cyproplex; *Braz.*: Andelux; Androcur; Androneo; Androsteron; Cetoteron; Ciprostat; Prostman; *Canad.*: Androcur; *China*: Androcur (色普龙); *Cz.*: Androcur; Cyproplex; Cysaxal; *Denm.*: Androcur; *Fin.*: Androcur; *Fr.*: Androcur; Kallale†; *Ger.*: Androcur; Virilit†; *Gr.*: Androcur; *Hong Kong*: Androcur; *Hung.*: Androcur; Cysaxal; *Indon.*: Androcur; *Irl.*: Androcur; *Israel*: Androcur; Cypron; *Ital.*: Androcur; *Malaysia*: Androcur; Cyproplex†; *Mex.*: Androcur; Bagopront†; Neoproxfl†; *Neth.*: Androcur; Curandron†; Cysaxal; *Norw.*: Androcur; *NZ*: Androcur†; Procur; Siterone; *Philipp.*: Androcur; *Pol.*: Androcur; *Port.*: Androcur; *Rus.*: Androcur (Андрокур); *S.Afr.*: Androcur; Cyproplex; *Singapore*: Androcur; Procur; *Spain*: Androcur; *Swed.*: Androcur; *Switz.*: Androbas†; Androcur; Elleacnelle; *Thai.*: Androcur; *Turk.*: Androcur; *UK*: Androcur; Cyprostat; *Ukr.*: Androfarm (Андрофарм); *Venez.*: Androcur; Asoteron.

Multi-ingredient Preparations. *Arg.*: Avancel; Biofem 35†; Climene; Diane; Mileva; Tess 35; Zinnia; *Austral.*: Brenda-35 ED; Climen†; Diane; Estelle; Juliet; Laila-35 ED; *Austria*: Bellgyn; Climen; Diane; Midane; Minerva; Xylia; *Belg.*: Claudia; Climen; Cyprodiol†; Daphne; Diane; Doccyproestra†; Docdonna†; Elisamylan; Gratiella; Ratiopharmeva†; *Braz.*: Artemidis; Ciprane; Climene; Diane; Diclin; Elamax; Ferane 35; Repopil; Selene; Tess; *Canad.*: CyEstra; Diane; *Chile*: Anuar; Climene; Diane; Dixi-35; Drina; Evilin; Lady-Ten 35; *China*: Climen (克龄蒙); Diane (达英); *Cz.*: Bellune; Chloe; Climen; Diane; Minerva; Vreya; *Denm.*: Diane; Dianova; Feminil; Vreya; Zafira†; Zyrona; *Fin.*: Cypreryl; Diane; Femilar; Feminil; Vreya; *Fr.*: Climene; Diane; Evepar; Holgyeme; Lumalia; Minerva; *Ger.*: Attempta; Bella†; Clevia†; Climen; Cyproderm; Cypronette†; Diane; Ergalea†; Morea; *Gr.*: Gynolen; *Hong Kong*: Climen 28†; Daphne; Diane; *Hung.*: Climen†; Cypromix; Diane; Minerva; *India*: Diane; Dinac; Frauline; Ginette; Krimson; *Indon.*: Climen 28; Diane; *Irl.*: Dianette; *Israel*: Diane; Estelle; *Ital.*: Climen; Diane; Pausene; Visofid; *Malaysia*: Climen; Diane; Estelle; Sucee; *Mex.*: Angie; Climene; Diane; Eunice 35-ED; Mileva; *Neth.*: Climene†; Diane; Minerva; Zypina†; *Norw.*: Diane; Feminil; Zyrona; *NZ*: Diane; Estelle; Ginet; *Philipp.*: Althea; Ancea; Climen 28; Crimson; Diane; *Pol.*: Chloe; Climen; Cyprest; Cyprodiol; CyproGen; Diane; OC-35; Syndi-35; *Port.*: Climen; Diane; *Rus.*: Bellune (Беллуне); Chloe (Хлое); Climen (Климен); Diane (Диане); *S.Afr.*: Adco-Fem; Claro; Climen; Diane; Diva; Ginette; Minerva; *Singapore*: Climen; Diane; Estelle; *Spain*: Climen; Diacaret; Dialider; Diane; Gyneplen; *Swed.*: Diane; Zyrona; *Switz.*: Climen; Cypestra; Cyprelle; Diane; Feminac; Holgyeme; Minerva; *Thai.*: Annie; B-Lady; Climen; Cypress; Dafne; Diane; Helen; Lady-35; Manoane; OC-35; Preme; Sucee; *Turk.*: Climen; Diane; Gynelle; *UK*: Acnocin; Cicafem; Clairette; Dianette; Diva; *Ukr.*: Climen (Климен); Diane-35 (Диане-35); *Venez.*: Climene; Diane; Dixi.

Pharmacopoeial Preparations

BP 2014: Cyproterone Tablets.

Danazol (BAN, USAN, pINN) ⊗

Danatsol; Danazolum; Win-17757; Даназол.

17α-Pregna-2,4-dien-20-yno[2,3-*d*]isoxazol-17β-ol.

$C_{22}H_{27}NO_2$=337.5

CAS — 17230-88-5.



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

USP 36: (Danazol). A white to pale yellow crystalline powder. Practically insoluble or insoluble in water and in petroleum spirit; sparingly soluble in alcohol and in benzene; soluble in acetone; freely soluble in chloroform; slightly soluble in ether. Store in airtight containers. Protect from light.

Uses and Administration

Danazol suppresses the pituitary-ovarian axis by inhibiting pituitary output of gonadotrophins. It has weak androgenic activity, and is described as an attenuated androgen.

Danazol has been given orally in the treatment of various conditions including endometriosis (p. 2264.1), some benign breast disorders such as mastalgia and fibrocystic breast disease (p. 2265.1), gynaecomastia (p. 2264.3), menorrhagia associated with dysfunctional uterine bleeding (p. 2265.2), and the prevention of hereditary angioedema (see p. 2265.1). It may also be used for the pre-operative thinning of the endometrium before hysteroscopic endometrial ablation. Danazol has been tried in other conditions including various blood and skin disorders (see below and p. 2265.2).

When given to women, treatment with danazol should be started on day 1 of the menstrual cycle or after pregnancy has been otherwise excluded.

In **endometriosis** the usual dose is 200 to 800 mg daily in 2 to 4 divided doses, adjusted according to the response. Therapy is given for 3 to 6 months or continued for up to 9 months if necessary.

In the treatment of **benign breast disorders** the usual initial dose is 100 to 400 mg daily in 2 divided doses, adjusted according to response, and continued for 3 to 6 months. For **gynaecomastia** 200 mg daily has been given to male adolescents, increased after 2 months to 400 mg daily if no response occurs; adult men have been given 400 mg daily initially, in up to 4 divided doses. Daily doses of up to 800 mg have been used, and therapy is usually tried for 6 months.

In dysfunctional uterine bleeding manifesting as **menorrhagia** doses of 200 mg daily have been given and treatment is reviewed after 3 months.

In the management of **hereditary angioedema** initial doses of 200 mg two or three times daily are given, and then reduced according to the patient's response. For doses used in children with hereditary angioedema, see p. 2265.1.

For **pre-operative thinning** of the endometrium danazol has been given in a dose of 400 to 800 mg daily in up to 4 divided doses, for 3 to 6 weeks.

Administration in children. Although the use of danazol is generally avoided in children, it has been given in the management of hereditary angioedema (see p. 2265.1) and to treat gynaecomastia in male adolescents (see above).

Blood disorders. Although danazol may produce thrombocytopenia and leucopenia its use has also been investigated in some blood disorders. Increased platelet counts have been reported in patients with *immune thrombocytopenia* (p. 1606.1). Small cohort studies have reported response rates of about 60 to 70%, including both partial and complete responses,[1-3] with a mean or median time to response of about 3 months.[1,2] Analysis of data from 96 patients suggested that age, sex, and spleen status may affect the response to danazol.[2] The response in men was not affected by age, but was better in splenectomised patients. However, in women there was a better response rate with advancing age in unsplenectomised patients, and the benefit of splenectomy on rates of response to danazol was only seen in younger women (45 years or younger). A better overall response rate in older patients (60 years and older) was also reported in another group.[4] However, others have found only a trend to less frequent response in younger patients, and no apparent relationship between response and sex or prior splenectomy.[1] *Thrombocytopenia associated with rheumatic disorders*, such as SLE, the antiphospholipid antibody syndrome, and rheumatoid arthritis has also been reported to respond to treatment with danazol.[5-7] For mention of the use of danazol in *Henoch-Schönlein purpura* see Hypersensitivity Vasculitis, p. 1606.1.

Additionally there have been reports of response to danazol therapy in patients with *auto-immune haemolytic anaemia*[8,9] (p. 1122.2), anaemia of *myelofibrosis with myeloid metaplasia*,[10] *paroxysmal nocturnal haemoglobinuria*,[11] *hereditary haemorrhagic telangiectasia*,[12] and *Evan's syndrome*

due to SLE.[13] There have been conflicting reports in patients with *myelodysplastic syndromes*.[14–18]

1. Maloisel F, *et al.* Danazol therapy in patients with chronic idiopathic thrombocytopenic purpura: long-term results. *Am J Med* 2004; 116: 590–4.
2. Ahn YS, *et al.* Long-term danazol therapy in autoimmune thrombocytopenia: unmaintained remission and age-dependent response in women. *Ann Intern Med* 1989; 111: 723–9.
3. Zimmer J, *et al.* Current management of adult idiopathic thrombocytopenic purpura in practice: a cohort study of 201 patients from a single center. *Clin Lab Haematol* 2004; 26: 137–42.
4. Andrès E, *et al.* Idiopathic thrombocytopenic purpura: a retrospective analysis in 139 patients of the influence of age on the response to corticosteroids, splenectomy and danazol. *Drugs Aging* 2003; 20: 841–6.
5. Blanco R, *et al.* Successful therapy with danazol in refractory autoimmune thrombocytopenia associated with rheumatic diseases. *Br J Rheumatol* 1997; 36: 1095–9.
6. Arnal C, *et al.* Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. *J Rheumatol* 2002; 29: 75–83.
7. Aviña-Zubieta JA, *et al.* Long-term effectiveness of danazol corticosteroids and cytotoxic drugs in the treatment of hematologic manifestations of systemic lupus erythematosus. *Lupus* 2003; 12: 52–7.
8. Ahn YS, *et al.* Danazol therapy for autoimmune hemolytic anemia. *Ann Intern Med* 1985; 102: 298–301.
9. Tan AM, *et al.* Danazol for treatment of refractory autoimmune hemolytic anaemia. *Ann Acad Med Singapore* 1989; 18: 707–9.
10. Cervantes F, *et al.* Efficacy and tolerability of danazol as a treatment for the anaemia of myelofibrosis with myeloid metaplasia: long-term results in 30 patients. *Br J Haematol* 2005; 129: 771–5.
11. Harrington WJ, *et al.* Danazol for paroxysmal nocturnal hemoglobinuria. *Am J Hematol* 1997; 54: 149–54.
12. Haq AU, *et al.* Hereditary hemorrhagic telangiectasia and danazol. *Ann Intern Med* 1988; 109: 171.
13. Aranegui P, *et al.* Danazol for Evan's syndrome due to SLE. *DICP Ann Pharmacother* 1990; 24: 641–2.
14. Wattel E, *et al.* Androgen therapy in myelodysplastic syndromes with thrombocytopenia: a report on 20 cases. *Br J Haematol* 1994; 87: 205–8.
15. Chabannon C, *et al.* A review of 76 patients with myelodysplastic syndromes treated with danazol. *Cancer* 1994; 73: 3073–80.
16. Letendre L, *et al.* Myelodysplastic syndrome treatment with danazol and cis-retinoic acid. *Am J Hematol* 1995; 48: 233–6.
17. Vinicu N, *et al.* Danazol therapy for thrombocytopenia in patients with myelodysplastic syndromes. *Acta Haematol (Basel)* 2002; 107: 234–6.
18. Chan G, *et al.* Danazol for the treatment of thrombocytopenia in patients with myelodysplastic syndrome. *Am J Hematol* 2002; 71: 166–71.

Endometriosis. Endometriosis is a condition affecting women mainly in their reproductive years, and caused by endometrial tissue developing outside the uterine cavity. It occurs most often in the pelvic peritoneal cavity and occasionally elsewhere such as the thoracic cavity. The aetiology is uncertain, although it is widely believed that retrograde flow of menstrual tissue introduces endometrial cells into the pelvic cavity, and that the implantation and growth of these cells may be influenced by genetic, immunologic, hormonal, and environmental factors.[1,2]

The presentation of endometriosis is variable, and while symptoms can range from mild to severe, many affected women are asymptomatic.[3] There is considerable overlap of symptoms with other conditions such as irritable bowel syndrome and pelvic inflammatory disease, but a definitive diagnosis of endometriosis can be made by visualisation at laparoscopy. The most common symptom is pain, usually manifesting as secondary dysmenorrhoea, dyspareunia, or cyclical back or pelvic pain. Pain may occur on micturition or defaecation if endometriosis affects the bladder or bowel; fibrosis and adhesions can develop. Endometriosis is also strongly associated with infertility. Severe endometriosis can distort the pelvic anatomy and thereby reduce fecundity, but how minimal and mild disease might affect fertility is unclear.[1,4] Management will depend in part on the presenting complaint, the extent of disease, and whether fertility is an issue. Conservative laparoscopic surgery or drug therapy may be used, but disease recurrence is common and long-term management is usually needed.[1,5] Nevertheless, spontaneous regression may occur in about a third of patients.[4,5]

Where **infertility** is the presenting symptom, surgery is generally performed in more severe disease, based on the assumption that correction of anatomical defects should improve fecundity although there is a lack of controlled studies to confirm this.[2,3,6,7] There is also limited evidence to suggest that surgery may improve fertility in mild disease,[3] but it is likely that the effect is small.[7] Assisted reproductive techniques such as IVF (see Infertility, p. 2253.1) offer the best chance of conception in more severe disease.[6,7] The extent of benefit in mild or moderate endometriosis is less clear.[6] Superovulation with intra-uterine insemination may be considered in such cases, with IVF an alternative for women aged 35 or more, and postoperative expectant management another option in younger women.[7]

Drug therapy has not been shown to be of direct value for infertility.[7,8] Also, because the drugs used for endometriosis tend to suppress ovulation and are potentially contraceptive, they will delay the opportunity for conception during treatment.[3,6,9] Pre- and postoperative drug therapy have also been tried, but there is insufficient evidence to show that these are any more effective than surgery alone.[10]

For patients whose primary symptom is **pain**, drug treatments that cause anovulatory hypoestrogenism (to induce atrophy and shrinkage of the hormonally sensitive ectopic endometrial deposits) are effective and are the mainstay of treatment.[4]

One of the most widely used treatments has been *danazol*, which produces subjective improvement in symptoms of pain and reduction of some pelvic abnormalities and tissue implants.[1,11] Its androgenic effects can be a problem and there is concern about its effect on blood lipids, therefore therapy is restricted to 6 months, or rarely up to 9 months. *Gestrinone* has been shown to be equally effective and may be a useful alternative.[3,8,12] *Progestogens* such as medroxyprogesterone acetate, dydrogesterone, or norethisterone acetate are also commonly used. They appear to be as effective as danazol in relieving pain symptoms[12] and tend to be better tolerated.[1,4] The use of local levonorgestrel from an intra-uterine device is also under investigation.[2,13]

Combined oral contraceptives are often used to relieve endometriosis pain, although the evidence for their benefit is largely observational[1] and data from controlled studies remain scanty.[14] They have been used in a continuous fashion to induce amenorrhoea, as well as the usual cyclical regimens, but it is unclear which is most effective.[3,8]

The other major group of drugs that are used in endometriosis are *gonadorelin analogues* such as buserelin, goserelin, leuprorelin, nafarelin, and triptorelin, which are as effective as danazol.[1,6,15] Long-term use is limited by the risk of osteoporosis, but concomitant 'add-back' therapy such as low-dose oestrogen and progestogen HRT,[1,3,6,8] or tibolone,[1,3] can be used to prevent this. Adverse effects resembling menopausal symptoms can also be relieved by 'add-back' therapy, which may make gonadorelin analogues more tolerable than danazol.[4] Parathyroid hormone[16,17] may also be effective for 'add-back' therapy to prevent bone loss.

Investigational drugs include the *antiprogestogens* such as mifepristone,[18] and *aromatase inhibitors* such as anastrozole and letrozole.[19]

There is some evidence that laparoscopic ablation can also reduce pain but controlled studies are limited.[4,6] Ideally, endometrial deposits found during diagnostic laparoscopy should be removed during the procedure.[3,8,20] There is a lack of comparison between surgery and drug treatment. Although there are reports of improved pain control using postoperative medical therapy,[20] study results have been mixed and there is insufficient evidence to confirm whether a combination of surgery and drug therapy has any additional benefit.[6,10]

There is a relatively high recurrence rate of endometriosis after conservative surgery and drug therapy. In women who can accept loss of child-bearing potential, definitive therapy is surgical oophorectomy and hysterectomy with complete excision or ablation of endometrial deposits.[3,8,20] Oestrogen replacement therapy is given, but carries a risk of recurrence of the disease; some have suggested that combined HRT may be preferable (see p. 2250.2).

1. Crosignani P, *et al.* Advances in the management of endometriosis: an update for clinicians. *Hum Reprod Update* 2006; 12: 179–89.
2. Hompes PGA, Mijatovic V. Endometriosis: the way forward. *Gynecol Endocrinol* 2007; 23: 5–12.
3. Royal College of Obstetricians and Gynaecologists. The investigation and management of endometriosis (green-top guideline no. 24, issued October 2006). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT24InvestigationEndometriosis2006.pdf (accessed 19/07/10)
4. Child TJ, Tan SL. Endometriosis: aetiology, pathogenesis and treatment. *Drugs* 2001; 61: 1735–50.
5. Farquhar C. Endometriosis. *BMJ* 2007; 334: 249–53.
6. Olive DL, Pritts EA. The treatment of endometriosis: a review of the evidence. *Ann N Y Acad Sci* 2002; 955: 360–72.
7. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility. *Fertil Steril* 2006; 86 (suppl 4): S156–S160.
8. European Society for Human Reproduction and Embryology. ESHRE guideline for the diagnosis and treatment of endometriosis (last updated 30th June, 2007). Available at: http://guidelines.endometriosis.org/index.html (accessed 30/06/08)
9. Hughes E, *et al.* Ovulation suppression for endometriosis for women with subfertility. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 10/11/09).
10. Yap C, *et al.* Pre and post operative medical therapy for endometriosis surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 30/06/08).
11. Selak V, *et al.* Danazol for pelvic pain associated with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/06/08).
12. Prentice A, *et al.* Progestagens and anti-progestagens for pain associated with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 30/06/08).
13. Vercellini P, *et al.* Endometriosis: current therapies and new pharmacological developments. *Drugs* 2009; 69: 649–75.
14. Davis L, *et al.* Modern combined oral contraceptives for pain associated with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).
15. Olive DL. Gonadotropin-releasing hormone agonists for endometriosis. *N Engl J Med* 2008; 359: 1136–42.
16. Finkelstein JS, *et al.* Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. *N Engl J Med* 1994; 331: 1618–23.
17. Finkelstein JS, *et al.* Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA* 1998; 280: 1067–73.
18. Kettel LM, *et al.* Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU 486). *Am J Obstet Gynecol* 1998; 178: 1151–6.
19. Ferrero S, *et al.* Pharmacological treatment of endometriosis: experience with aromatase inhibitors. *Drugs* 2009; 69: 943–52.
20. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. *Fertil Steril* 2008; 90 (suppl 3): S260–S269.

Gynaecomastia. Gynaecomastia is a common benign glandular enlargement of the male breast, caused either by increased oestrogenic activity or decreased androgenic activity. Examples of gynaecomastia caused by increased oestrogenic activity include oestrogen-secreting malignancies, increased aromatisation of androgens into oestrogens (associated with an increase in adipose tissue), and exposure to drugs with oestrogenic activity such as digitoxin. Neonatal and pubertal gynaecomastia also come into this category, the former due to exposure to maternal oestrogens and the latter because oestrogen levels increase before androgens do. Gynaecomastia caused by decreased androgenic activity may be associated with the natural decline of testosterone concentrations in ageing men, various forms of hypogonadism, increased metabolism of androgens (for example in alcoholism), and exposure to drugs with anti-androgenic properties such as spironolactone, cimetidine, ketoconazole, cyproterone acetate, or flutamide. Some systemic disorders may also be associated with gynaecomastia, including cirrhosis of the liver, hyperthyroidism, and renal failure; it may also occur on refeeding after starvation.

Gynaecomastia has a high rate of spontaneous regression, and specific therapy (other than the removal of any cause) need only be considered if the enlarged breast tissue causes sufficient pain, embarrassment, or emotional discomfort to interfere with the patient's daily life.[1–3] Drug therapy is only likely to be of benefit while tissue is still proliferating; once glandular tissue has become inactive and fibrotic (usually after more than 12 months) a complete response is unlikely.[2,3]

Except in primary hypogonadism,[3] testosterone itself is unlikely to be of benefit (and may be aromatised to oestradiol, exacerbating the situation),[2] but a non-aromatisable androgen such as *androstanolone* (dihydrotestosterone) may produce some benefit.[2,4] *Danazol* has produced marked responses in some patients,[4] but adverse effects may limit its usefulness.[2] Quite good responses have also been reported with *tamoxifen*,[4–6] and this has been recommended as a drug of choice.[2,3] A retrospective review[7] of men treated for idiopathic gynaecomastia found that a complete response occurred in 18 of 23 men treated with tamoxifen, but in only 8 of 20 who received danazol. The decrease in pain was similar for both groups, but relapse occurred in 5 of the men treated with tamoxifen. The use of other drugs with anti-oestrogen effects, such as *clomifene*[8,9] and *raloxifene*,[6] has also been described in small numbers of boys with pubertal gynaecomastia. Aromatase inhibitors have been investigated for their potential to prevent the peripheral aromatisation of androgens to oestrogens. Improvement in pubertal gynaecomastia has been reported with *testolactone*,[10] but a controlled study[11] in 80 boys found 6 months of treatment with *anastrozole* to be no better than placebo. Studies in men being treated for prostate cancer also found anastrozole to be ineffective for the prevention[12,13] and treatment[12] of gynaecomastia associated with bicalutamide therapy; in comparison, tamoxifen was effective in both studies.

Where drug therapy is unsuccessful, or the breast enlargement is long-standing, surgical removal of breast tissue is advocated.[2,3] Prophylactic low-dose radiotherapy to the breast can significantly reduce the risk of gynaecomastia and breast pain in men undergoing anti-androgen treatment for prostate cancer,[2] although comparative studies suggest that it may be less effective than tamoxifen.[14,15]

1. Bembo SA, Carlson HE. Gynecomastia: its features, and when and how to treat it. *Cleve Clin J Med* 2004; 71: 511–17.
2. Gikas P, Mokbel K. Management of gynaecomastia: an update. *Int J Clin Pract* 2007; 61: 1209–15.
3. Braunstein GD. Gynecomastia. *N Engl J Med* 2007; 357: 1229–37.
4. Gruntmanis U, Braunstein GD. Treatment of gynecomastia. *Curr Opin Investig Drugs* 2001; 2: 643–9.
5. McDermott MT, *et al.* Tamoxifen therapy for painful idiopathic gynecomastia. *South Med J* 1990; 83: 1283–5.
6. Lawrence SE, *et al.* Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. *J Pediatr* 2004; 145: 71–6.
7. Ting ACW, *et al.* Comparison of tamoxifen with danazol in the management of idiopathic gynecomastia. *Am Surg* 2000; 66: 38–40.
8. LeRoith D, *et al.* The effect of clomiphene citrate on pubertal gynaecomastia. *Acta Endocrinol (Copenh)* 1980; 95: 177–80.
9. Plourde PV, *et al.* Clomiphene in the treatment of adolescent gynecomastia: clinical and endocrine studies. *Am J Dis Child* 1983; 137: 1080–2.
10. Zachmann M, *et al.* Treatment of pubertal gynaecomastia with testolactone. *Acta Endocrinol (Copenh)* 1986; 279 (suppl): 218–26.
11. Plourde PV, *et al.* Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2004; 89: 4428–33.
12. Saltzstein D, *et al.* Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. *Prostate Cancer Prostatic Dis* 2005; 8: 75–83.
13. Boccardo F, *et al.* Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol* 2005; 23: 808–15.

14. Perdonà S, *et al.* Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. *Lancet Oncol* 2005; 6: 295–300.
15. Di Lorenzo G, *et al.* Gynecomastia and breast pain induced by adjuvant therapy with bicalutamide after radical prostatectomy in patients with prostate cancer: the role of tamoxifen and radiotherapy. *J Urol (Baltimore)* 2005; 174: 2197–2203.

Hereditary angioedema. Danazol may be given to prevent attacks of hereditary angioedema (p. 2485.2). Oral doses of 200 mg once or twice daily are typically used, but may range from 100 mg three times each week up to 400 mg twice daily.[1] The lowest effective prophylactic dose should be used to minimise adverse effects from long-term use.[2] Different regimens have been described, starting with either high (400 to 600 mg daily) or low (200 mg daily) induction doses that are gradually adjusted according to response, with the aim of reaching a maintenance dose of about 50 mg daily.[3] Short-term prophylaxis may be given in situations expected to provoke an attack, such as surgery or dental procedures, when complement C1 esterase inhibitor is not available. Danazol 100 to 600 mg daily may be given, starting 5 days before the procedure and continuing for 48 hours after.[1,3] Attenuated androgens are not usually given in the acute management of hereditary angioedema. However, the early use of up to 1 g daily of danazol may shorten the duration of an attack of peripheral swelling.[1]

Attenuated androgens are also generally avoided in children because of adverse effects. They may be considered when other treatments are ineffective,[4] and may be helpful in children with frequent abdominal attacks occurring more than once a month.[1] The use of the lowest effective dose, an intermittent regimen, and careful monitoring have been advocated.[1,4] Long-term prophylactic doses of danazol 50 to 200 mg daily (or 2.5 mg/kg daily) have been used, and should be given even less frequently in alternate-day or twice-weekly regimens if possible. Short-term prophylaxis before surgery or dental procedures has been given in doses of 300 mg daily (or 5 mg/kg daily), from 5 days before until 48 hours after the procedure. Similarly,[4] doses of 5 mg/kg daily for 2 or 3 days may be used as short-term prophylaxis in the presence of other precipitating factors, such as infection. As for adults, attenuated androgens are not usually given in the acute management of hereditary angioedema, but early doubling of the long-term prophylactic dose in use may be considered in mild attacks, and continued until the patient has been asymptomatic for 48 hours.

Patients with lupus erythematosus-like syndromes associated with hereditary angioedema have also benefited from danazol therapy.[5–7]

1. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; 139: 379–94. Correction. *ibid.*; 141: 189–90. [dose]
2. Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema. *Allergy Asthma Proc* 2008; 29: 225–31.
3. Bowen T, *et al.* Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Ann Allergy Asthma Immunol* 2008; 100 (suppl 2): S30–S40.
4. Parkas H, *et al.* Management of hereditary angioedema in pediatric patients. Abstract: *Pediatrics* 2007; 120: 635. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/3/e713 (accessed 10/12/09)
5. Masse R, *et al.* Reversal of lupus-erythematosus-like disease with danazol. *Lancet* 1980; ii: 651.
6. Donaldson VH, Hess EV. Effect of danazol on lupus-erythematosus-like disease in hereditary angioneurotic oedema. *Lancet* 1980; ii: 1145.
7. Dubra P, *et al.* Discoid lupus erythematosus associated with hereditary angioneurotic oedema. *Br J Dermatol* 1990; 123: 241–4.

Mastalgia. Mastalgia may occur alone or be associated with nodularity or other fibrocystic changes in the female breast. It is usually divided into cyclical mastalgia, which accounts for about two-thirds of all cases, non-cyclical mastalgia, and chest-wall or costochondral pain (Tietze's syndrome). Cyclical mastalgia has a temporal association with the menstrual cycle and is most common in the third decade of life, with a chronic relapsing course thereafter; it usually resolves at the menopause. Non-cyclical mastalgia tends to present later in life as constant or intermittent pain that is not associated with the menstrual cycle.

Once clear pathological causes of pain have been excluded most patients can be managed by simple reassurance.[1–3] In the management of mild mastalgia, simple measures such as wearing a properly fitting brassiere and the use of relaxation techniques are widely recommended.[1–3] Warm compresses or ice packs and gentle massage may provide relief, particularly when the pain is cyclic or intermittent and of short duration.[1] There is some evidence that a low-fat diet may reduce symptoms of mastalgia, but the evidence to support a restriction of dietary caffeine intake is inconsistent and such a measure is not generally recommended.[1,3] Although few studies have been done to confirm a beneficial effect, many women are likely to self-medicate as required with simple analgesics such as paracetamol and oral or topical NSAIDs.[1] Patients who take an oral contraceptive or HRT may find that symptoms improve on reducing the estrogen dose or stopping treatment.[1,3]

Women with moderate to severe mastalgia that has lasted for more than 6 months may require specific drug treatment. *Danazol* is probably the most effective drug for mastalgia, and studies suggest that it is of benefit in about 70% or more of patients with cyclical mastalgia,[1–3] and somewhat fewer with the non-cyclical form.[2] However, adverse effects may force the dose to be reduced or stopped. Danazol given only during the luteal phase (days 14 to 28) has been reported to be effective in cyclical mastalgia, and to cause few adverse effects.[4] *Gestrinone* has also been reported to be effective in cyclical mastalgia.[1] Although effective in cyclical mastalgia,[3,5] *bromocriptine* is not as effective as danazol, and its use is similarly limited by adverse effects.[1,2] A small study[6] has reported that *lisuride* was effective in cyclical mastalgia.

Gamolenic acid (usually as evening primrose oil) has been widely used in cyclical mastalgia because of early studies suggesting that it was an effective treatment with few adverse effects. Although further studies have produced conflicting results and there is now doubt about its efficacy,[2,3,5] some still suggest that it can be tried as there may be a beneficial effect with minimal risk.[1]

In refractory cyclical or non-cyclical mastalgia *tamoxifen*[3,5] has been shown to be effective; controlled studies have reported efficacy rates of up to 96% in cyclical mastalgia and 56% in non-cyclical mastalgia.[1] However, the concept of using tamoxifen in otherwise healthy premenopausal women has produced some concern.[7–9] *Toremifene* has been reported to be of benefit.[10,11] *Goserelin* has also been shown to be effective,[12,13] but there is limited experience with the use of gonadorelin analogues and severe adverse effects are likely to limit their use.[1] Injection of a *local anaesthetic* with a *corticosteroid* has proved effective for the pain of non-cyclical mastalgia.[14]

Other drugs that have been used for cyclical mastalgia include antibacterials, diuretics, and various vitamins but there is no evidence that they are any better than placebo.[1]

1. Smith RL, *et al.* Evaluation and management of breast pain. *Mayo Clin Proc* 2004; 79: 353–72.
2. Gumm R, *et al.* Evidence for the management of mastalgia. *Curr Med Res Opin* 2004; 20: 681–4.
3. Rosolowich V, *et al.* Society of Obstetricians and Gynecologists of Canada. Mastalgia. *J Obstet Gynaecol Can* 2006; 28: 49–57. Also available at: http://www.sogc.org/guidelines/public/170E-CPG-January2006.pdf (accessed 30/06/08)
4. O'Brien PMS, Abukhalil IEH. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. *Am J Obstet Gynecol* 1999; 180: 18–23.
5. Srivastava A, *et al.* Evidence-based management of mastalgia: a meta-analysis of randomised trials. *Breast* 2007; 16: 503–12.
6. Kaleli S, *et al.* Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo-controlled randomized study. *Fertil Steril* 2001; 75: 718–23.
7. Anonymous. Tamoxifen for benign breast disease. *Lancet* 1986; i: 305.
8. Smallwood JA, Taylor I. Tamoxifen for mastalgia. *Lancet* 1986; i: 680–1.
9. Fentiman IS, *et al.* Tamoxifen for mastalgia. *Lancet* 1986; i: 681.
10. Gong C, *et al.* A double-blind randomized controlled trial of toremifen therapy for mastalgia. *Arch Surg* 2006; 141: 43–7.
11. Oksa S, *et al.* Toremifene for premenstrual mastalgia: a randomised, placebo-controlled crossover study. *BJOG* 2006; 113: 713–18.
12. Hamed H, *et al.* LHRH analogue for treatment of recurrent and refractory mastalgia. *Ann R Coll Surg Engl* 1990; 72: 221–4.
13. Mansel RE, *et al.* European randomized, multicenter study of goserelin (Zoladex) in the management of mastalgia. *Am J Obstet Gynecol* 2004; 191: 1942–9.
14. Khan HN, *et al.* Local anaesthetic and steroid combined injection therapy in the management of non-cyclical mastalgia. *Breast* 2004; 13: 129–32.

Menorrhagia. Danazol is effective in the treatment of menorrhagia (p. 2300.3) but it is only used short term because of its adverse effects.[1] It may also be used for pre-operative endometrial thinning.[2]

1. Beaumont H, *et al.* Danazol for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).
2. Sowter MC, *et al.* Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2002 (accessed 30/06/08).

Premenstrual syndrome. Danazol may be useful[1–3] in the management of the premenstrual syndrome (p. 2272.3), but some have found it to be of value only for cyclical mastalgia rather than for general symptoms,[4] and in any case adverse effects limit its long-term use.

1. Halbreich U, *et al.* Elimination of ovulation and menstrual cyclicity (with danazol) improves dysphoric premenstrual syndromes. *Fertil Steril* 1991; 56: 1066–9.
2. Deeny M, *et al.* Low dose danazol in the treatment of the premenstrual syndrome. *Postgrad Med J* 1991; 67: 450–4.
3. Hahn PM, *et al.* A randomized, placebo-controlled, crossover trial of danazol for the treatment of premenstrual syndrome. *Psychoneuroendocrinology* 1995; 20: 193–209.
4. O'Brien PMS, Abukhalil IEH. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. *Am J Obstet Gynecol* 1999; 180: 18–23.

Skin disorders. Danazol has been reported to relieve pruritus (p. 1687.3) refractory to usual treatment with antihistamines; underlying conditions have included cholinergic urticaria,[1,2] chronic actinic dermatitis,[3] myeloproliferative disorders,[4] and auto-immune disorders.[4] In 2 reports, the skin disorder had been associated with low plasma concentrations of antiprotease.[1,3] Danazol has generally been given in oral doses of 200 to 800 mg daily.[4] Maintenance treatment may be needed, and relapse can occur when the dose is reduced or treatment is withdrawn.

Danazol was also reported to reduce induration and pain in a man with lipodermatosclerosis.[5]

1. Berth-Jones J, Graham-Brown RAC. Cholinergic pruritus, erythema and urticaria: a disease spectrum responding to danazol. *Br J Dermatol* 1989; 121: 235–7.
2. La Sheli MS, England RW. Severe refractory cholinergic urticaria treated with danazol. *J Drugs Dermatol* 2006; 5: 664–7.
3. Humbert P, *et al.* Chronic actinic dermatitis responding to danazol. *Br J Dermatol* 1991; 124: 195–7.
4. Kolodny L, *et al.* Danazol relieves refractory pruritus associated with myeloproliferative disorders and other diseases. *Am J Hematol* 1996; 51: 112–16.
5. Hafner C, *et al.* Lipodermatosclerosis: successful treatment with danazol. *Acta Derm Venereol* 2005; 85: 365–6.

Adverse Effects

Adverse effects of danazol that reflect inhibition of the pituitary-ovarian axis include menstrual disturbances and amenorrhoea (occasionally persistent), hot flushes, sweating, reduction in breast size, changes in libido, vaginal dryness and irritation, emotional lability, and nervousness.

Adverse effects attributable to androgenic activity include acne, oily skin or hair, mild hirsutism, oedema, weight gain, deepening of the voice, androgenic alopecia, and rarely clitoral hypertrophy. Testicular atrophy and a reduction in spermatogenesis may occur.

Other adverse effects include gastrointestinal disturbances, increased or decreased blood cell counts, thrombotic events, headache, backache, dizziness, tremor, depression, fatigue, sleep disorders, muscle spasm or cramp, rash, hyperglucagonaemia, abnormal glucose tolerance, decreased serum high-density-lipoprotein cholesterol, increased serum low-density-lipoprotein cholesterol, and elevation of liver-function test values and rarely cholestatic jaundice. Some patients may have palpitations, tachycardia, and hypertension. Benign intracranial hypertension and visual disturbances have occurred.

Effects on carbohydrate metabolism. Diabetes mellitus developed in a patient 8 weeks after starting danazol 400 mg twice daily for endometriosis[1] and resolved completely after the drug was stopped.

1. Seifer DB, *et al.* Insulin-dependent diabetes mellitus associated with danazol. *Am J Obstet Gynecol* 1990; 162: 474–5.

Effects on the liver. As with other 17α-alkylated steroids (see p. 2308.1), hepatic adverse effects have been associated with danazol, including hepatitis[1] and cholestasis.[2,3] Hepatic adenoma has occurred after long-term danazol use.[4–7] Adenomas are often removed surgically because of the risks of haemorrhage and malignant transformation, but regression over 18 months and 2 years after stopping danazol has been described in 2 patients.[6] There have also been rare reports of focal nodular hyperplasia,[7,8] hepatocellular carcinoma,[9] and peliosis hepatis.[10]

A case of acute hepatic failure has been attributed to danazol in a patient already taking ciclosporin (see p. 2266.1).

1. Ohsawa T, Iwashita S. Hepatitis associated with danazol. *Drug Intell Clin Pharm* 1986; 20: 889.
2. Boue F, *et al.* Danazol and cholestatic hepatitis. *Ann Intern Med* 1986; 105: 139–40.
3. Bray GP, *et al.* Resolution of danazol-induced cholestasis with S-adenosylmethionine. *Postgrad Med J* 1993; 69: 237–9.
4. Fermand JP, *et al.* Danazol-induced hepatocellular adenoma. *Am J Med* 1990; 88: 529–30.
5. Bork K, *et al.* Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. *Lancet* 1999; 353: 1066–7.
6. Bork K, Schneiders V. Danazol-induced hepatocellular adenoma in patients with hereditary angio-oedema. *J Hepatol* 2002; 36: 707–9.
7. Bartley J, *et al.* Hepatocellular adenoma and focal nodular hyperplasia after long-term use of danazol for endometriosis: a case report. *Arch Gynecol Obstet* 2004; 269: 290–3.
8. Helsing P, Nielsen EW. Hepatocellular focal nodular hyperplasia after danazol treatment for hereditary angio-oedema. *Acta Derm Venereol* 2006; 86: 272–3.
9. Confavreux C, *et al.* Danazol-induced hepatocellular carcinoma. *Q J Med* 2003; 96: 317–18.
10. Makdisi WJ, *et al.* Patal pellosis of the liver and spleen in a patient with agnogenic myeloid metaplasia treated with danazol. *Am J Gastroenterol* 1995; 90: 317–8.

Effects on the pancreas. There have been reports of pancreatitis in patients receiving danazol.[1,2]

1. Chevalier X, *et al.* Danazol induced pancreatitis and hepatitis. *Clin Rheumatol* 1990; 9: 239–41.
2. Balasch J, *et al.* Acute pancreatitis associated with danazol treatment for endometriosis. *Hum Reprod* 1994; 9: 1163–5.

Effects on the skin and hair. There have been isolated reports of erythema multiforme occurring in patients given danazol. In 3 cases the reaction developed about 2 weeks after starting danazol, and was effectively managed by stopping danazol and treating with corticosteroids.[1,2]

Hirsutism is a recognised adverse effect of danazol, but is usually mild. Excessive facial hair growth of sudden onset,

sufficient to cause distress, has been described in a woman given danazol for mastalgia. The hirsutism improved after stopping the danazol.[3]

1. Gately LE, Andes WA. Danazol and erythema multiforme. *Ann Intern Med* 1988; 109: 85.
2. Reynolds NJ, Sansom JE. Erythema multiforme during danazol therapy. *Clin Exp Dermatol* 1992; 17: 140.
3. Zawar V, Sankalecha C. Facial hirsutism following danazol therapy. *Cutis* 2004; 74: 301–3.

Precautions

Danazol should be used with caution in conditions that may be adversely affected by fluid retention, such as in cardiovascular, hepatic, and renal disorders; it should be avoided in marked dysfunction. It should also be used with care in patients with diabetes mellitus, polycythaemia, abnormal blood lipids, migraine, or epilepsy. Danazol should not be given to patients with undiagnosed genital bleeding or androgen-dependent tumours. As with other 17α-alkylated compounds, there is an increased risk of liver disorders and liver function should be monitored during therapy. It should not be used in patients with a thromboembolic disorder or a history of thrombosis.

Danazol should not be given during pregnancy because of a possible androgenic effect on the female fetus (see below), and non-hormonal contraception is recommended during treatment. Caution is required in children and adolescents since precocious sexual development may occur in boys and virilisation in girls, and premature epiphyseal closure may occur in both sexes.

In the event of androgenic effects, danazol should be withdrawn, as they may prove irreversible on continued use.

Breast feeding. Licensed product information warns that danazol should be avoided in breast-feeding women because of the theoretical potential for androgenic effects in the infant.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies danazol 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 06/10/11)

Pregnancy. Reports of masculinisation of female infants born to mothers who had received danazol during pregnancy.[1-3]

1. Shaw RW, Farquhar JW. Female pseudohermaphroditism associated with danazol exposure in utero: case report. *Br J Obstet Gynaecol* 1984; 91: 386–9.
2. Kingsbury AC. Danazol and fetal masculinization: a warning. *Med J Aust* 1985; 143: 410–11.
3. Brunskill PJ. The effects of fetal exposure to danazol. *Br J Obstet Gynaecol* 1992; 99: 212–15.

Interactions

Therapy with danazol may inhibit the hepatic metabolism of several drugs including carbamazepine (see p. 517.3), ciclosporin (see below), and possibly tacrolimus (see p. 1973.2). Danazol may also enhance the effects of warfarin (see Sex Hormones under Warfarin, p. 1535.1). Introduction of danazol appeared to reduce the maintenance requirement for alfacalcidol (see p. 2118.1). Rhabdomyolysis has been attributed to use of danazol with statins (see p. 1495.2).

Ciclosporin. Danazol may raise ciclosporin concentrations (see p. 1955.1), possibly by inhibiting its metabolism.

A case of fatal acute hepatic failure due to centrilobular massive hepatic necrosis was attributed to danazol in a patient already taking ciclosporin.[1] Danazol may have raised the ciclosporin concentrations in this case, but the authors speculated that an alternative interaction between the two drugs might have played a role in this reaction to danazol.

1. Hayashi T, *et al.* Fatal acute hepatic failure induced by danazol in a patient with endometriosis and aplastic anemia. *J Gastroenterol* 2001; 36: 783–6.

Pharmacokinetics

Danazol is absorbed from the gastrointestinal tract and metabolised in the liver; absorption is markedly increased if it is taken with food. A plasma elimination half-life of 3 to 6 hours has been reported after a single dose, but is increased to about 26 hours with repeated dosing. Ethisterone, 2-hydroxymethylethisterone, and 17-hydroxymethylethisterone are the major metabolites, though none have pituitary inhibiting activity. Danazol and its metabolites may undergo enterohepatic circulation. Metabolites are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ladogal; *Austral.*: Azol; Danocrine†; *Austria*: Danokrin; *Belg.*: Danatrol; *Braz.*: Ladogal; *Canad.*: Cyclomen; *China*: Gong Fu Yi Kang (宫福伊康); *Cz.*: Danoval; *Fr.*: Danatrol; *Gr.*: Danatrol; *Hong Kong*: Anargil; Azol†; Danocrine; *Hung.*: Danoval; *India*: Benzol; Danogen; Endozol; Gonablok; Gynadom; Gynazol; Gynodan; Ladogal; Zendol; *Indon.*: Azol; Danocrine; *Irl.*: Danol†; *Israel*: Danol; *Ital.*: Danatrol; *Jpn*: Bonzol; *Malaysia*: Anargil; Azol†; Ladogal; Nazol; *Mex.*: Danalem; Ladogal; Novaprin; *Neth.*: Danatrol; *NZ*: Azol; D-Zol†; *Philipp.*: Ladogal; *Port.*: Danatrol; *Rus.*: Danol (Данол); Danoval (Дановал); *S.Afr.*: Danogen; Ladazol; *Singapore*: Azol†; Ladogal; Nazol; *Spain*: Danatrol; *Switz.*: Danatrol†; *Thai.*: Anargil; Ectopal; Ladogal; Vabon; *Turk.*: Danasin; *UK*: Danol; *Venez.*: Danogen; Ladogal.

Pharmacopoeial Preparations
USP 36: Danazol Capsules.

Degarelix *(BAN, USAN, rINN)*

Dégarélix; Degarelixum; FE-200486 (degarelix or degarelix acetate); Дегареликс.

N-Acetyl-3-(naphthalen-2-yl)-D-alanyl-4-chloro-D-phenylalanyl-3-(pyridin-3-yl)-D-alanyl-L-seryl-4-({[(4*S*)-2,6-dioxohexahydropyrimidin-4-yl]carbonyl}amino)-L-phenylalanyl-4-(carbamoylamino)-D-phenylalanyl-L-leucyl-N^6-(1-methylethyl)-L-lysyl-L-prolyl-D-alaninamide.

$C_{82}H_{103}ClN_{18}O_{16}$=1632.3

CAS — 214766-78-6.

ATC — L02BX02.

ATC Vet — QL02BX02.

UNII — SX0XJI3A11.

Degarelix Acetate *(USAN, rINNM)*

Acetato de degarelix; Dégarélix, Acétate de; Degarelixi Acetas; FE-200486 (degarelix or degarelix acetate); Дегареликс Ацетат.

$C_{82}H_{103}ClN_{18}O_{16}.xC_2H_4O_2.nH_2O$

CAS — 934246-14-7.

ATC — L02BX02.

ATC Vet — QL02BX02.

UNII — 118S89P20R.

Uses and Administration

Like cetrorelix (p. 2257.2), degarelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is used to reduce testosterone concentrations in the hormonal therapy of advanced prostate cancer (p. 712.3). Degarelix is given as the acetate, but doses are expressed in terms of the base. It is given as a subcutaneous depot injection in the abdominal area. An initial dose of degarelix 240 mg is given in two separate injections of 120 mg, as a solution of 40 mg/mL. Maintenance doses of 80 mg are then given once every 28 days, as a solution of 20 mg/mL.

References.

1. Van Poppel H, *et al.* Degarelix: a novel gonadotropin-releasing hormone (GnRH) receptor blocker—results from a 1-yr, multicentre, randomised, phase 2 dosage-finding study in the treatment of prostate cancer. *Eur Urol* 2008; 54: 805–13.
2. Gittelman M, *et al.* Degarelix Study Group. A 1-year, open label, randomized phase II dose finding study of degarelix for the treatment of prostate cancer in North America. *J Urol (Baltimore)* 2008; 180: 1986–92.
3. Klotz L, *et al.* The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008; 102: 1531–8.
4. Frampton JE, Lyseng-Williamson KA. Degarelix. *Drugs* 2009; 69: 1967–76.
5. Steinberg M. Degarelix: a gonadotropin-releasing hormone antagonist for the management of prostate cancer. *Clin Ther* 2009; 31: 2312–31.

Adverse Effects and Precautions

Injection site reactions of pain and erythema are very common with degarelix, while swelling, induration, and nodules occur less often but may still be common. Transient chills, fever, and flu-like symptoms may occur hours after dosing. Other effects commonly reported for degarelix have included increases in liver enzyme values, insomnia, dizziness, headache, and gastrointestinal disturbances.

Hot flushes are a very common consequence of androgen suppression by degarelix, while night sweats, fatigue, and weight gain are common complaints. Degarelix can also contribute to loss of libido, erectile dysfunction, testicular atrophy, and gynaecomastia. Long-term androgen deprivation therapy in general has also been associated with prolongation of the QT interval and decreases in bone density.

Pharmacokinetics

Degarelix is about 90% bound to plasma proteins. It undergoes peptide hydrolysis in the hepato-biliary system, and is mainly excreted as peptide fragments in the faeces. About 20 to 30% of a dose is renally excreted. Degarelix is injected to form a subcutaneous depot, and the pharmacokinetics of the drug is strongly influenced by the concentration of the injected solution. After subcutaneous injection of 240 mg at a concentration of 40 mg/mL, degarelix has a terminal half-life of about 43 to 53 days; after maintenance doses of 80 mg as 20 mg/mL the half-life is about 28 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Firmagon; *Austria*: Firmagon; *Belg.*: Firmagon; *Canad.*: Firmagon; *Cz.*: Firmagon; *Denm.*: Firmagon; *Fr.*: Firmagon; *Ger.*: Firmagon; *Gr.*: Firmagon; *Irl.*: Firmagon; *Israel*: Firmagon; *Jpn*: Gonax; *Neth.*: Firmagon; *Norw.*: Firmagon; *Pol.*: Firmagon; *Port.*: Firmagon; *Swed.*: Firmagon; *Switz.*: Firmagon; *UK*: Firmagon; *USA*: Firmagon.

Delmadinone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de delmadinona; Delmadinona, acetato de; Delmadinonacetat; Delmadinone, Acétate de; Delmadinoni Acetas; Delmadinoniasetaatti; RS-1301; Дельмадинона Ацетат.

6-Chloro-17α-hydroxypregna-1,4,6-triene-3,20-dione acetate.

$C_{23}H_{27}ClO_4$=402.9

CAS — 15262-77-8 (delmadinone); 13698-49-2 (delmadinone acetate).

ATC Vet — QG03DX91.

UNII — 92833M0LD9.

Profile

Delmadinone acetate is a progestogen with anti-androgenic and anti-oestrogenic activity. It is used as an anti-androgen in veterinary practice.

Deslorelin *(BAN, USAN, rINN)* ⊗

Deslorelina; Desloréline; Deslorelinum; D-Trp LHRH-PEA; Деслорелин.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

$C_{64}H_{83}N_{17}O_{12}$=1282.5

CAS — 57773-65-6.

ATC Vet — QH01CA93.

UNII — TKG3166TVE.

Profile

Deslorelin is an analogue of gonadorelin (p. 2280.2) that has been investigated in the treatment of precocious puberty, short stature, prostate cancer, and endometriosis.

References.

1. Anonymous. Deslorelin: D-Trp-LHRH-PEA, LHRH agonist analogue, Somagard. *Drugs R D* 1999; 2: 420–2.
2. Klein KO, *et al.* Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; 86: 4711–16.
3. Yanovski JA, *et al.* Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med* 2003; 348: 908–17.
4. Weise M, *et al.* Determinants of growth during gonadotropin-releasing hormone analog therapy for precocious puberty. *J Clin Endocrinol Metab* 2004; 89: 103–7.

Desogestrel *(BAN, USAN, rINN)*

Desogestreeli; Désogestrel; Desogestrelum; Dezogestrel; Org-2969; Дезогестрел.

13β-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17β-ol.

$C_{22}H_{30}O$=310.5

CAS — 54024-22-5.

ATC — G03AC09.

ATC Vet — QG03AC09.

UNII — 81K9V7M3A3.

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

Ph. Eur. 8: (Desogestrel). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane; very soluble in methyl alcohol.

Uses and Administration

Desogestrel is a progestogen (see Progesterone, p. 2300.2) structurally related to levonorgestrel that is used as a hormonal contraceptive (see p. 2231.3). A typical daily dose of 150 micrograms is used as the progestogenic component

of monophasic combined oral contraceptive preparations. Doses of 50 to 150 micrograms daily may be used in triphasic combined preparations. A dose of 75 micrograms daily is used as an oral progestogen-only contraceptive; unlike traditional progestogen-only contraceptives, desogestrel is said to reliably inhibit ovulation. Progestogen-only contraceptive efficacy is reduced if a dose of desogestrel is delayed by more than 12 hours.

Contraception. The effects of a progestogen-only contraceptive containing desogestrel have been reported.[1-3] Oral desogestrel has also been investigated as a male contraceptive, combined with testosterone given by intramuscular injection,[4] subcutaneous implant,[5,6] or transdermal patch.[7]

1. Collaborative study group on the desogestrel-containing progestogen-only pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. *Eur J Contracept Reprod Health Care* 1998; 3: 169–78.
2. Rice CF, *et al.* A comparison of the inhibition of ovulation achieved by desogestrel 75 micrograms and levonorgestrel 30 micrograms daily. *Hum Reprod* 1999; 14: 982–5.
3. Korver T, *et al.* Maintenance of ovulation inhibition with the 75-microgram desogestrel-only contraceptive pill (Cerazette) after scheduled 12-h delays in tablet intake. *Contraception* 2005; 71: 8–13.
4. Wu FCW, *et al.* Oral progestogen combined with testosterone as a potential male contraceptive: additive effects between desogestrel and testosterone enanthate in suppression of spermatogenesis, pituitary-testicular axis, and lipid metabolism. *J Clin Endocrinol Metab* 1999; 84: 112–22.
5. Kinniburgh D, *et al.* Oral desogestrel with testosterone pellets induces consistent suppression of spermatogenesis to azoospermia in both Caucasian and Chinese men. *Hum Reprod* 2002; 17: 1490–1501.
6. Anderson RA, *et al.* Investigation of hormonal male contraception in African men: suppression of spermatogenesis by oral desogestrel with depot testosterone. *Hum Reprod* 2002; 17: 2869–77.
7. Bair WM, *et al.* A novel male contraceptive pill-patch combination: oral desogestrel and transdermal testosterone in the suppression of spermatogenesis in normal men. *J Clin Endocrinol Metab* 2001; 86: 5201–9.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3. When used as a progestogen-only contraceptive, irregular bleeding is more common with desogestrel than with other progestogen-only preparations. Desogestrel is reported to have few androgenic effects, and to have less adverse effect on the serum lipid profile than older 19-nortestosterone derivatives. However, there is some evidence that desogestrel-containing combined oral contraceptives are associated with a small increased risk of venous thromboembolism (see p. 2238.1, and for precautions, see p. 2241.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desogestrel in combined hormonal contraceptives 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 04/10/11)

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

After oral doses, desogestrel undergoes oxidative transformation in the intestinal mucosa and liver to its active metabolite 3-keto-desogestrel (etonogestrel—see p. 2277.3).

References.

1. Madden S, *et al.* Metabolism of the contraceptive steroid desogestrel by the intestinal mucosa. *Br J Clin Pharmacol* 1989; 27: 295–9.
2. Madden S, *et al.* Metabolism of the contraceptive steroid desogestrel by human liver in vitro. *J Steroid Biochem* 1990; 35: 281–8.
3. Kuhnz W, *et al.* Protein binding of the contraceptive steroids gestodene, 3-keto-desogestrel and ethinyloestradiol in human serum. *J Steroid Biochem* 1990; 35: 313–18.
4. Kuhnz W, *et al.* Pharmacokinetics and serum protein binding of 3-keto-desogestrel in women during three cycles of treatment with a low-dose combination oral contraceptive. *Arzneimittelforschung* 1992; 42: 1142–6.
5. Timmer CJ, *et al.* Bioavailability and bioequivalence of etonogestrel from two oral formulations of desogestrel: Cerazette and Lisela. *Eur J Drug Metab Pharmacokinet* 1999; 24: 335–43.
6. Verhoeven CH, *et al.* Excretion and metabolism of desogestrel in healthy postmenopausal women. *J Steroid Biochem Mol Biol* 2001; 78: 471–80.
7. Kothonen T, *et al.* The role of CYP2C and CYP3A in the disposition of 3-keto-desogestrel after administration of desogestrel. *Br J Clin Pharmacol* 2005; 60: 69–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Camelia; Carmin; Cerazette; Lumilac; *Austria*: Cerazette; *Belg.*: Cerazette; Lueva; *Braz.*: Cerazette; Kelly; *Chile*: Arlette; Cerazette; Lactafem; Nogesta; Vanish; *Cz.*: Azalia; Cerazette; Fleur; *Denm.*: Cerazet; Cerazette; Nacrez; *Fin.*: Cerazette; *Fr.*: Cerazette; *Ger.*: Cerazette; *Gr.*: Cerazette; *Hong Kong*: Cerazette; *Hung.*: Azalia; Cerazette; *India*: Cerazette; *Indon.*: Cerazette; *Irl.*: Cerazette; *Israel*: Cerazette; *Ital.*: Cerazet; Cerazette; *Mex.*: Cerazette; *Neth.*: Cerazette; *Norw.*: Cerazette; *NZ*: Cerazette; *Philipp.*: Cerazette; *Pol.*: Azalia; Cerazette; *Port.*: Cerazette; *Rus.*: Cerazette (Цэрозетта); Lactinette (Лактинет); *Spain*: Azalia; Cerazet; *Swed.*: Cerazette; *Switz.*: Cerazette; *Thai.*: Cerazette; *UK*: Aizea; Cerazette; Cerelle; Zelleta; *Ukr.*: Cerazette (Цэрозетта); Lactinette (Лактинет); *Venez.*: Arlette; Cerazette.

Multi-ingredient Preparations. *Arg.*: Marvelon; Mercilon; *Austral.*: Marvelon; *Austria*: Gracial; Liberel; Marvelon; Mercilon; *Belg.*: Desorelle†; Gracial; Marvelon; Mercilon; Ovidol; *Braz.*: Femina; Gestradiol; Gracial; Malu; Mercilon Conti; Mercilon; Microdiol; Minian; Novial; Primera; Primeravinte†; *Canad.*: Apri; Linessa; Marvelon; Ortho-Cept; *Chile*: Ciclidon; Conti-Marvelon; Dal; Desoren; Gracial; Gynostat; Marvelon; Midalet; Miniestrel; Neolette; *China*: Mercilon (美欣乐); *Cz.*: Adele; Gracial; Laurina; Marvelon; Mercilon; Natalya; Novynette; Regulon; Tricia; *Denm.*: Daisynelle; Desorelle; Femelle; Femigen; Femistad; Gracial; Marvelon; Mercilon; Novynette; *Fin.*: Gracial; Laurina; Marvelon; Mercilon; *Fr.*: Cycleane†; Desobel; Mercilon; Varnoline; *Ger.*: Biviol; Cyclosa†; Desmin; Lamuna†; Lovelle; Marvelon; Novial; Oviala; Oviol†; *Gr.*: Gracial; Laurina; Marvelon; Mercilon; *Hong Kong*: Gracial; Marvelon; Mercilon; Novynette; *Hung.*: Gracial; Laurina; Marvelon; Mercilon; Novynette; Regulon; Samba; *India*: Femilon; Locpil; Novelon; *Indon.*: Marvelon; Mercilon; *Irl.*: Gracial; Leticia; Marviol; Mercilon; Vivides; *Israel*: Feminet; Mercilon; Microdiol; *Ital.*: Dueva; Gracial; Lucille; Mercilon; Novynette; Planum; Practil; Securgin; *Malaysia*: Marvelon; Mercilon; Novynette; Regulon; *Mex.*: Desmin; Detegen; Marvelon; Mercilon; Novial; *Neth.*: Gracial; Juliane; Laurina; Lonicera; Marvelon; Mercilon; Ovidol†; *Norw.*: Marvelon; Mercilon; *NZ*: Marvelon; Mercilon; *Philipp.*: Gracial; Marvelon; Mercilon; *Pol.*: Marvelon; Mercilon; Novynette; Regulon; *Port.*: Gracial; Laurina; Marvelon; Mercilon; Novynette; Regulon; *Rus.*: Marvelon (Марвелон); Mercilon (Мерсилон); Novynette (Новинет); Regulon (Регулон); Tri-Merci (Три-Мерси); *S.Afr.*: Marvelon; Mercilon; *Singapore*: Marvelon; Mercilon; *Spain*: Bemasive; Gracial; Microdiol; Regulon; Suavuret; *Swed.*: Desolett; Mercilon; Trimiron†; *Switz.*: Desoren; Gradal; Marvelon; Mercilon; *Thai.*: Daisy; Marvelon; Mercilon; Minny; Novynette; Oilezz; *Turk.*: Desolett; Myralon; *UK*: Cimizt; Gedarel; Marvelon; Mercilon; *Ukr.*: Marvelon (Марвелон); Mercilon (Мерсилон); Novynette (Новинет); Regulon (Регулон); Tri-Merci (Три-Мерси); *USA*: Apri; Azurette; Caziant; Cesia; Cyclessa; Desogen; Kariva; Mircette; Ortho-Cept; Reclipsen; Solia; Velivet; Viorele; *Venez.*: Ciclidon; Marvelon; Mercilon; Mipil; Novial.

Pharmacopoeial Preparations
BP 2014: Desogestrel Tablets;
USP 36: Desogestrel and Ethinyl Estradiol Tablets.

Dienestrol *(BAN, rINN)*

Dehydrostilbestrol; Dienestrol; Dienestroli; Dienestrolis; Dienestrolum; Dienoestrol; Dienoestrolum; Dienösztrol; Oestrodienolum; Диенэстрол.

(E,E)-4,4'-[Di(ethylidene)ethylene]diphenol; 4,4'-(1,2-Diethylidene-1,2-ethanediyl)bisphenol.

$C_{18}H_{18}O_2$=266.3

CAS — 84-17-3 (dienestrol); 13029-44-2 ((E,E)-dienestrol).

ATC — G03CB01.

ATC Vet — QG03CB01; QG03CC02.

UNII — RRW32X4U1F.

Pharmacopoeias. In *US*.

USP 36: (Dienestrol). Colourless, white, or practically white needle-like crystals, or white or practically white crystalline powder. It is odourless. Practically insoluble in water; soluble in alcohol, in acetone, in ether, in methyl alcohol, in propylene glycol, and in solutions of alkali hydroxides; slightly soluble in chloroform and in fatty oils.

Profile

Dienestrol is a synthetic nonsteroidal oestrogen structurally related to diethylstilbestrol (below). It has been used as a vaginal cream in the treatment of menopausal atrophic vaginitis. If used on a long-term basis in women with a uterus a progestogen is required.

Dienestrol diacetate has been used as an ingredient of topical preparations for skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Ortho-Dienestrol†.

Pharmacopoeial Preparations
USP 36: Dienestrol Cream.

Dienogest *(BAN, USAN, rINN)*

Dienogest; Dienogestil; Dienogestum; STS-557; Диеногест.

17-Hydroxy-3-oxo-19-nor-17α-pregna-4,9-diene-21-nitrile.

$C_{20}H_{25}NO_2$=311.4

CAS — 65928-58-7.

UNII — 46M3EV8HHE.

Profile

Dienogest is a nonethinylated progestogen (see Progesterone, p. 2300.2) structurally related to nortestosterone. It is reported to have anti-androgenic properties. Dienogest is used as the progestogen component of some combined oral contraceptives (see p. 2231.3). A dose of 2 mg daily is typically used in monophasic preparations, and doses of 2 or 3 mg daily may be found in multiphasic sequential preparations. It is also used as the progestogen component in menopausal HRT (see p. 2244.1) in a daily dose of 2 mg. In the management of endometriosis (p. 2264.1) an oral dose of dienogest 2 mg daily is used; it is given in a continuous regimen regardless of menstrual bleeding.

Reviews.

1. Foster RH, Wilde MI. Dienogest. *Drugs* 1998; 56: 825–33.
2. Wellington K, Perry CM. Estradiol valerate/dienogest. *Drugs* 2002; 62: 491–504.
3. Hoy SM, Scott LJ. Estradiol valerate/dienogest: in oral contraception. *Drugs* 2009; 69: 1635–46.
4. Pérez-Campos EF. Ethinylestradiol/dienogest in oral contraception. *Drugs* 2010; 70: 681–9.
5. McCormack PL. Dienogest: a review of its use in the treatment of endometriosis. *Drugs* 2010; 70: 2073–88.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dienogest and oestrogen combinations 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 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Visanne; *Austria*: Visanne; *Canad.*: Visanne; *Cz.*: Visanne; *Denm.*: Visanne; *Fin.*: Visanne; *Ger.*: Visanne; *Gr.*: Visannette; *Hung.*: Visanne; *Israel*: Visabelle; *Jpn*: Dinagest; *Neth.*: Visanne; *Norw.*: Visanne; *Port.*: Visanne; *Singapore*: Visanne; *Spain*: Visannette; *Swed.*: Visanne; *Switz.*: Visanne.

Multi-ingredient Preparations. *Arg.*: Dienopil; Florence; Rubi; *Austral.*: Qlaira; Valette; *Austria*: Motion; Qlaira; Valette; *Belg.*: Climodien; Qlaira; *Chile*: Gianda; Tinelle; *Cz.*: Dienille; Dienorette; Jeanine; Klimodien; Qlaira; *Denm.*: Climodien†; Qlaira; *Fin.*: Qlaira; *Fr.*: Climodiene; Qlaira; *Ger.*: Climodien; Lafamme; Maxim; Qlaira; Valette; *Gr.*: Climodien; Qlaira; *Hung.*: Dienille; Qlaira; *Irl.*: Qlaira; *Israel*: Qlair; *Ital.*: Klaira; *Neth.*: Climodien; Lafamme; Qlaira; *Norw.*: Climodien†; Qlaira; *Pol.*: Atywia; Jeanine; Qlaira; *Port.*: Climodien; Lafamme; Qlaira; Valette; *Rus.*: Climodien (Климодиен); Jeanine (Жанин); *Singapore*: Qlaira; *Spain*: Ailyn; Climodien; Danielle; Donabel; Mevaren; Qlaira; *Swed.*: Climodien†; Qlaira; *Turk.*: Climodien; *UK*: Qlaira; *Ukr.*: Jeanine (Жанин); Klimodien (Климодиен)†; Silhouette (Силуэт); *USA*: Natazia.

Diethylstilbestrol *(BAN, rINN)*

DES; Diéthylstilbestrol; Diethylstilbestrolum; Diethylstilboestrol; Dietilestilbestrol; Dietilstilbestrolis; Dietilstilbösztrol; Dietylstilbestrol; Dietyylistilbestroli; Estilbestrol; NSC-3070; Stilbestrol; Stilboestrol; Диэтилстильбэстрол.

(E)-αβ-Diethylstilbene-4-4'-diol.

$C_{18}H_{20}O_2$=268.4

CAS — 56-53-1.

ATC — G03CB02; L02AA01.

ATC Vet — QG03CB02; QG03CC05; QL02AA01.

UNII — 731DCA35BT.

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

Ph. Eur. 8: (Diethylstilbestrol). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 36: (Diethylstilbestrol). A white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in chloroform, in ether, in fatty oils, and in dilute alkali hydroxides. Store in airtight containers. Protect from light.

Diethylstilbestrol Dipropionate *(BANM, rINNM)*

Diethylstilbestrol Dipropionate de; Diethylstilbestroli Dipropionas; Dietilestilbestrol dipropionato de; Dipropionato de dietilestilbestrol; Stilboestrol Dipropionate; Диэтилстильбэстрола дипропионат.

(E)-αβ-Diethylstilbene-4,4'-diol dipropionate.

$C_{24}H_{28}O_4$=380.5

CAS — 130-80-3.

ATC — G03CB02; L02AA01.

ATC Vet — QG03CB02; QL02AA01.
UNII — Y98CK3J0OL.

Uses and Administration

Diethylstilbestrol is a synthetic nonsteroidal oestrogen that has been used in the palliation of breast and prostate cancer.

Daily oral doses of 10 to 20 mg are occasionally used in the palliative treatment of malignant neoplasms of the breast (p. 702.1) in postmenopausal women. The usual oral dose in carcinoma of the prostate (p. 712.3) is 1 to 3 mg daily; higher doses were formerly given. Diethylstilbestrol has also been used in the treatment of prostatic carcinoma in the form of its diphosphate salts (see Fosfestrol, p. 2279.1).

Diethylstilbestrol has been used as pessaries in the short-term management of menopausal atrophic vaginitis.

Adverse Effects and Precautions

Dose-related adverse effects of diethylstilbestrol include nausea, fluid retention, and arterial and venous thrombosis, and these effects are common at the doses used for palliation of cancer. Impotence and gynaecomastia occur in men, and withdrawal bleeding may occur in women, as may hypercalcaemia and bone pain in women treated for breast cancer. Diethylstilbestrol should be used with caution in those with cardiovascular disease or renal or hepatic impairment. Use of diethylstilbestrol is contra-indicated if pregnancy is suspected.

Adverse effects and precautions of oestrogens in general (steroidal compounds) are covered under Estradiol, on p. 2273.2.

Historically, high doses of diethylstilbestrol and related substances were used for 'hormonal support' in pregnant women to try to prevent miscarriages and preterm births, most commonly in the USA. This practice was later shown to be ineffective. Adverse effects on the genito-urinary tract of offspring of these women have been noted. In particular, an increased incidence of changes in the cervix and vagina including adenosis and rarely clear-cell adenocarcinoma has been seen in postpubertal daughters of women who received diethylstilbestrol or related substances during pregnancy (see below). A possible increased incidence of abnormalities of the genital tract and of abnormal spermatozoa has been reported in male offspring similarly exposed (see below). The recipients themselves appear to be at a small increased risk of breast cancer (see below).

Carcinogenicity. *BREAST.* No statistically significant difference in the incidence of breast cancer was found among a group of 693 women given diethylstilbestrol during pregnancy 25 years earlier compared with a control group of 668 who were not.[1] This finding was, however, criticised[2] on the basis that the study lacked the statistical power to reject the null hypothesis. In another study[3] the incidence of breast cancer in 3033 women who had taken diethylstilbestrol in pregnancy during the period 1940 to 1960 was compared with the incidence in a comparable group of unexposed women. This study involved over 85 000 women-years of follow-up in each group and it was found that the incidence of breast cancer per 100 000 women-years was 134 in the exposed group and 93 in the unexposed group (a relative risk of 1.4). The authors concluded that in those women given diethylstilbestrol there was a moderately increased incidence of breast cancer but that some unrecognised concomitant of exposure could not be excluded as a possibility for the increase. Although this study suggested that the risk increased over time, subsequent follow-up,[4] while confirming a modest increase in risk overall, did not confirm a higher risk in these women as time went on. Further follow-up and analysis[5] of the combined data from these cohort studies[1,3,4] confirmed a modest increase in risk of breast cancer associated with diethylstilbestrol (relative risk 1.27, 95% confidence interval 1.07 to 1.52). Another large population cohort study[6] suggested that the risk of fatal breast cancer might also be increased in women who had been given diethylstilbestrol.

Two cases of breast cancer[7] in premenopausal women exposed to diethylstilbestrol *in utero* have raised the possibility that the risk of breast cancer may be increased in these women, in addition to the known genito-urinary risk (see below under Pregnancy, Effects on Female Offspring). However, a cohort study[8] involving 4536 women exposed *in utero* found no increased risk of other cancers overall, and did not show an increased risk of breast cancer (relative risk 1.18; 95% confidence intervals 0.56 to 2.49). A later study[9] of further follow-up of this cohort, plus additional data from another group, found that although the risk overall and for younger women was not increased, from the age of 40 years the risk increased to 1.91 (95% confidence interval 1.09 to 3.33). The risk appeared to increase further with greater age, but the relatively small number of cases in women aged 50 years and over made this harder to establish.

1. Bibbo M, *et al.* A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. *N Engl J Med* 1978; 298: 763–7.
2. Clark LC, Portier KM. Diethylstilbestrol and the risk of cancer. *N Engl J Med* 1979; 300: 263–4.
3. Greenberg ER, *et al.* Breast cancer in mothers given diethylstilbestrol in pregnancy. *N Engl J Med* 1984; 311: 1393–8.
4. Colton T, *et al.* Breast cancer in mothers prescribed diethylstilbestrol in pregnancy. *JAMA* 1993; 269: 2096–2100.
5. Titus-Ernstoff L, *et al.* Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer* 2001; 84: 126–33.
6. Calle EE, *et al.* Diethylstilbestrol and risk of fatal breast cancer in a prospective cohort of US women. *Am J Epidemiol* 1996; 144: 645–52.
7. Huckell C, *et al.* Premenopausal breast cancer after in-utero exposure to stilboestrol. *Lancet* 1996; 348: 331.
8. Hatch EE, *et al.* Cancer risk in women exposed to diethylstilbestrol in utero. *JAMA* 1998; 280: 630–4.
9. Palmer JR, *et al.* Prenatal diethylstilbestrol exposure and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 1509–14.

GENITO-URINARY TRACT. See below under Pregnancy, Effects on Female Offspring.

KIDNEY. Renal carcinoma was associated with the long-term use of diethylstilbestrol for prostate cancer in 2 men.[1]

1. Nissenkorn I, *et al.* Oestrogen-induced renal carcinoma. *Br J Urol* 1979; 51: 6–9.

LIVER. Hepatic angiosarcoma developed in a 76-year-old man who had received diethylstilbestrol 3 mg daily for 12 years.[1] Hepatoma developed in another elderly man who had received a similar dose for 4.5 years.[2]

1. Hoch-Ligeti C. Angiosarcoma of the liver associated with diethylstilbestrol. *JAMA* 1978; 240: 1510–11.
2. Brooks JJ. Hepatoma associated with diethylstilbestrol therapy for prostate carcinoma. *J Urol (Baltimore)* 1982; 128: 1044–5.

Effects on the blood. Adverse haematological effects reported with diethylstilbestrol have included severe bone-marrow changes in a 71-year-old man given diethylstilbestrol in a massive dose of 150 mg daily for 7 years[1] and fatal immune haemolytic anaemia in a 69-year-old man given weekly infusions of diethylstilbestrol 1 g for 9 weeks.[2] The latter reaction was due to an IgG antibody specific for diethylstilbestrol.

1. Anderson AL, Lynch EC. Myelodysplopoietic syndrome associated with diethylstilbestrol therapy. *Arch Intern Med* 1980; 140: 976–7.
2. Rosenfeld CS, *et al.* Diethylstilbestrol-associated hemolytic anemia with a positive direct antiglobulin test result. *Am J Med* 1989; 86: 617–18.

Pregnancy. *EFFECTS ON FEMALE OFFSPRING.* The DESAD (Diethylstilbestrol and Adenosis) Project carried out by the National Cancer Institute in the USA led to several reports linking exposure to diethylstilbestrol *in utero* to adverse genital-tract effects.[1-3] It was reported that of nearly 300 young females with clear-cell adenocarcinoma of the genital tract, more than 80% had been exposed *in utero* to diethylstilbestrol-type hormones.[1] Patients had been aged 7 to 28 years at the time of diagnosis. Doses and duration of treatment varied widely; the association existed for both 1.5 mg of diethylstilbestrol daily throughout pregnancy and variable amounts for a week or more during the first trimester. Vaginal adenosis, rare in unexposed young women, was present in about a third of those exposed in the first 4 months of pregnancy, and cervical ectropion in more than two-thirds. Vaginal epithelial changes were most closely associated with early exposure to diethylstilbestrol, with the total dose, and with the duration of exposure; their incidence decreased with age. The risk of cancer in the first 25 years after exposure was small.[2] Fertility did not appear to be impaired in women who had been exposed *in utero* to diethylstilbestrol but the relative risk of an unfavourable outcome of pregnancy in such a group was 1.69. However, of the women who became pregnant, 81% of those exposed to diethylstilbestrol and 95% of control subjects had at least one full-term live birth.[3] In a review of vaginal adenosis and its association with maternal diethylstilbestrol ingestion during pregnancy[4] it was noted that the link between diethylstilbestrol and particularly the benign changes in the vagina and cervix (adenosis) seemed well established. The association between this drug and the development of genital malignancies was less clear, and the very low incidence in the prospective studies in the USA supported this concept. The problem was rare in the UK, but clinicians should be aware that it existed. Cases of vaginal adenosis in young women should be investigated and screened appropriately, and preferably referred to centres where colposcopic expertise was available. Treatment of simple vaginal adenosis should be avoided.

Later reviews[5,6] have highlighted the fact that adverse effects were still emerging in women who had been exposed to diethylstilbestrol *in utero* several decades before. The need for thorough medical screening of such women was emphasised; genital-tract examination was particularly important. It was pointed out[6] that many women exposed to diethylstilbestrol *in utero* were in the reproductive stage of their lives and warranted special observation since a diethylstilbestrol-damaged genital tract posed a potential problem during pregnancy.[5,6] It has also been suggested, for example, that such women are at increased risk of developing pre-eclampsia.[7,8]

There has been concern about the possibility of transgenerational effects on the grandchildren of women given diethylstilbestrol during pregnancy. There has been very little reported on *female offspring of exposed women*, but there were no breast or gynaecological abnormalities found on examination of 28 daughters (over 15 years of age) of women who had been exposed *in utero* and had in many cases cervical and/or vaginal changes characteristic of diethylstilbestrol exposure.[9] Limited data from a Dutch cohort[10] of 16 284 mothers and 8934 sons suggested that the *male offspring of exposed women* may in turn be at greatly increased risk of hypospadias, although the absolute risk was small. A case-control study[11] also found an increased risk, but of a much smaller magnitude, and another cohort study[12] (including DESAD data) found no support for a greatly increased risk of hypospadias. The earlier cohort study that reported the greatly increased risk may have been affected by factors related to infertility, as the study was done in a cohort of subfertile women, about half of whom had undergone IVF.

Further information on the adverse effects of diethylstilbestrol in females exposed to the drug *in utero* can be obtained from the references listed below.[13-23] For mention of the possible increased risk of breast cancer in these women, see Carcinogenicity, above.

1. Professional and Public Relations Committee of the DESAD (Diethylstilbestrol and Adenosis) Project of the Division of Cancer Control and Rehabilitation. Exposure in utero to diethylstilbestrol and related synthetic hormones: association with vaginal and cervical cancers and other abnormalities. *JAMA* 1976; 236: 1107–9.
2. O'Brien PC, *et al.* Vaginal epithelial changes in young women enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) Project. *Obstet Gynecol* 1979; 53: 300–8.
3. Barnes AB, *et al.* Fertility and outcome of pregnancy in women exposed in utero to diethylstilbestrol. *N Engl J Med* 1980; 302: 609–13.
4. Emens M. Vaginal adenosis and diethylstilboestrol. *Br J Hosp Med* 1984; 31: 42–8.
5. Anonymous. Diethylstilboestrol—effects of exposure in utero. *Drug Ther Bull* 1991; 29: 49–50.
6. Wingfield M. The daughters of stilboestrol. *BMJ* 1991; 302: 1414–15.
7. Mittendorf R, Williams MA, Stilboestrol exposure in utero and risk of pre-eclampsia. *Lancet* 1995; 345: 265–6.
8. Troisi R, *et al.* Preeclampsia risk in women exposed in utero to diethylstilbestrol. *Obstet Gynecol* 2007; 110: 113–20.
9. Kaufman RH, Adam E. Findings in female offspring of women exposed in utero to diethylstilbestrol. *Obstet Gynecol* 2002; 99: 197–200.
10. Klip H, *et al.* Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. *Lancet* 2002; 359: 1102–7.
11. Brouwers MM, *et al.* Hypospadias: a transgenerational effect of diethylstilbestrol? *Hum Reprod* 2006; 21: 666–9.
12. Palmer JR, *et al.* Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology* 2005; 16: 583–6.
13. Herbst AL, *et al.* Prenatal exposure to stilbestrol: a prospective comparison of exposed female offspring with unexposed controls. *N Engl J Med* 1975; 292: 334–9.
14. Herbst AL, *et al.* Age-incidence and risk of diethylstilbestrol-related clear cell adenocarcinoma of the vagina and cervix. *Am J Obstet Gynecol* 1977; 128: 43–50.
15. Kaufman RH, *et al.* Upper genital tract changes associated with in-utero exposure to diethylstilbestrol. *Am J Obstet Gynecol* 1977; 128: 51–9.
16. Fowler WC, Edelman DA. In utero exposure to DES: evaluation and followup of 199 women. *Obstet Gynecol* 1978; 51: 459–63.
17. Anderson B, *et al.* Development of DES-associated clear-cell carcinoma: the importance of regular screening. *Obstet Gynecol* 1979; 53: 293–9.
18. Noller KL, *et al.* Maturation of vaginal and cervical epithelium in women exposed in utero to diethylstilbestrol (DESAD project). *Am J Obstet Gynecol* 1983; 146: 279–85.
19. Robboy SJ, *et al.* Increased incidence of cervical and vaginal dysplasia in 3980 diethylstilbestrol-exposed young women: experience of the National Collaborative Diethylstilbestrol Adenosis Project. *JAMA* 1984; 252: 2979–83.
20. Kaufman RH, *et al.* Upper genital tract changes and infertility in diethylstilbestrol-exposed women. *Am J Obstet Gynecol* 1986; 154: 1312–18.
21. Melnick S, *et al.* Rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix—an update. *N Engl J Med* 1987; 316: 514–16.
22. Helmerhorst TJM, *et al.* Colposcopic findings and intraepithelial neoplasia in diethylstilbestrol-exposed offspring: the Dutch experience. *Am J Obstet Gynecol* 1989; 161: 1191–4.
23. Giusti RM, *et al.* Diethylstilbestrol revisited: a review of the long-term health effects. *Ann Intern Med* 1995; 122: 778–88.

EFFECTS ON MALE OFFSPRING. The effects of exposure to diethylstilbestrol *in utero* have been studied in male offspring.[1-4] Problems in passing urine and abnormalities of the penile urethra were found to be more common in young males exposed to diethylstilbestrol *in utero* than in controls in one study.[1] In another,[2] genital tract abnormalities such as epididymal cysts, capsular induration, and defective testicles occurred in 41 of 163 diethylstilbestrol-exposed men compared with 11 of 168 controls; sperm counts and motility were also reduced in exposed males. In contrast, comparison of 828 men exposed to diethylstilbestrol *in utero* with 676 unexposed men suggested that, overall, diethylstilbestrol exposure did not result in an increased risk of genito-urinary abnormalities, infertility, or testicular cancer.[3] It was suggested that previously reported increased frequencies of such abnormalities may have resulted from a selection bias and/or from a difference in diethylstilbestrol usage. Another study[4] in 253 exposed men found that although there was an increased incidence of congenital malformations of the genitalia (18 cases compared with 5 of 241 controls), this was not associated with any decrease in fertility or impairment of sex-

ual function. An analysis[5] of the combined data from 4 cohorts suggested that there was a small increase in the risk of infertility (relative risk 1.3, 95% confidence interval 1.0 to 1.6) in men who had been exposed to diethylstilbestrol, but that overall this was not associated with an increased likelihood of never fathering a pregnancy or live birth, and did not affect the number of pregnancies or live births. Data from these 4 cohorts were also analysed[6] for the development of cancer. The overall rates of cancer were similar to those in unexposed men and to national rates. The rate of testicular cancer was increased in men who had been exposed to diethylstilbestrol *in utero*, but this finding did not reach statistical significance and was limited to only one of the cohorts. Further follow-up will be needed as these men approach the age at which most cancers are diagnosed.

For reference to possible effects on the male *grandchildren* of women who took diethylstilbestrol (the offspring of women exposed *in utero*) see Effects on Female Offspring, p. 2268.2.

1. Henderson BE, *et al.* Urogenital tract abnormalities in sons of women treated with diethylstilbestrol. *Pediatrics* 1976; 58: 505–7.
2. Anonymous. Offspring of women given DES remains under study. *JAMA* 1977; 238: 932.
3. Leary FJ, *et al.* Males exposed in utero to diethylstilbestrol. *JAMA* 1984; 252: 2984–9.
4. Wilcox AJ, *et al.* Fertility in men exposed prenatally to diethylstilbestrol. *N Engl J Med* 1995; 332: 1411–16.
5. Perez KM, *et al.* National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril* 2005; 84: 1649–56.
6. Strohsnitter WC, *et al.* Cancer risk in men exposed in utero to diethylstilbestrol. *J Natl Cancer Inst* 2001; 93: 545–51.

Veterinary use. In the EU, the use of diethylstilbestrol or other stilbenes in veterinary medicine is banned unless prior steps are taken to ensure the treated animal and its products are not available for human or animal consumption.

Pharmacokinetics

Diethylstilbestrol is readily absorbed from the gastrointestinal tract. It is slowly metabolised in the liver and excreted in the urine and faeces, mainly as the glucuronide.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gobbibestrol; Novo Fosfostilben†; *Braz.*: Destilbenol; *Fr.*: Distilbene; *Gr.*: Distilbene; *Irl.*: Boestrol†; *Mex.*: Dimeprost.

Multi-ingredient Preparations. *China*: Fukexin (复可欣).

Pharmacopoeial Preparations
BP 2014: Diethylstilbestrol Pessaries; Diethylstilbestrol Tablets;
USP 36: Diethylstilbestrol Injection; Diethylstilbestrol Tablets.

Drospirenone *(BAN, USAN, rINN)*

Dihydrospirenone; Drospirenon; Drospirenona; Drospirénone; Drospirenoni; Drospirenonum; SH-470; ZK-30595; Дроспиренон.

(6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-Hexadecahydro-10,13-dimethylspiro[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5′*H*)-furan]-3,5′(2*H*)-dione.

$C_{24}H_{30}O_3$=366.5

CAS — 67392-87-4.

UNII — NP95J34A25.

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

Ph. Eur. 8: (Drospirenone). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in dichloromethane.

USP 36: (Drospirenone). A white to off-white powder. Practically insoluble in water and in hexane; sparingly soluble in alcohol and in ethyl acetate; soluble in methyl alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Drospirenone is a structural analogue of spironolactone (p. 1499.3); it has the effects of a progestogen (see Progesterone, p. 2300.2) with antimineralocorticoid and anti-androgenic activity. It is used as the progestogenic component of combined oral contraceptives (see p. 2231.3), usually in a dose of 3 mg daily with ethinylestradiol 30 micrograms, for 21 days of each 28-day cycle. A combination of drospirenone 3 mg with ethinylestradiol 20 micrograms, given daily for 24 days of each 28-day cycle, may also be used for contraception and for the management of premenstrual dysphoric disorder (see Premenstrual Syndrome, below) or moderate acne (p. 1682.2) in women who also require an oral contraceptive. Drospirenone is also used as the progestogenic component of menopausal HRT (see below) in a continuous dosage regimen of 0.5 or 2 mg daily.

Reviews.

1. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. *Contraception* 2000; 62: 29–38.
2. Sitruk-Ware R. Pharmacology of different progestogens: the special case of drospirenone. *Climacteric* 2005; 8 (suppl 3): 4–12.
3. Oelkers WH. Drospirenone in combination with estrogens: for contraception and hormone replacement therapy. *Climacteric* 2005; 8 (suppl 3): 19–27.
4. Fenton C, *et al.* Drospirenone/ethinylestradiol 3mg/20 μg (24/4 day regimen): a review of its use in contraception, premenstrual dysphoric disorder and moderate acne vulgaris. *Drugs* 2007; 67: 1749–65.
5. Blitzer J, Paoletti AM. Added benefits and user satisfaction with a low-dose oral contraceptive containing drospirenone: results of three multicentre trials. *Clin Drug Investig* 2009; 29: 73–8.

Contraception. References.

1. Huber J, *et al.* Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone. *Eur J Contracept Reprod Health Care* 2000; 5: 25–34.
2. Foidart JM, *et al.* A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. *Eur J Contracept Reprod Health Care* 2000; 5: 124–34. Correction. *ibid.* 2001; 6: 63.
3. Parsey KS, Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. *Contraception* 2000; 61: 105–11.
4. Oelkers W, *et al.* Effect of an oral contraceptive containing drospirenone on the renin-angiotensin-aldosterone system in healthy female volunteers. *Gynecol Endocrinol* 2000; 14: 204–13.
5. Bachmann G, *et al.* Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20 micrograms ethinylestradiol and 3 mg drospirenone. *Contraception* 2004; 70: 191–8.
6. Gruber DM, *et al.* A comparison of the cycle control, safety, and efficacy profile of a 21-day regimen of ethinylestradiol 20 μg and drospirenone 3mg with a 21-day regimen of ethinylestradiol 20 μg and desogestrel 150 μg. *Treat Endocrinol* 2006; 5: 115–21.
7. Cibula D, *et al.* Efficacy and safety of a low-dose 21-day combined oral contraceptive containing ethinylestradiol 20 μg and drospirenone 3mg. *Clin Drug Investig* 2006; 26: 143–50.

Menopausal disorders. Drospirenone is used as the progestogenic component of menopausal HRT[1-4] (p. 2244.2). The antimineralocorticoid effect of drospirenone has also been investigated and found to lower blood pressure in postmenopausal women with treated and untreated hypertension.[5]

1. Schürmann R, *et al.* Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric* 2004; 7: 189–96.
2. Whitehead M. Hormone replacement therapy with estradiol and drospirenone: an overview of the clinical data. *J Br Menopause Soc* 2006; 12 (suppl 1): 4–7.
3. Archer DF, *et al.* Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. *Menopause* 2005; 12: 716–27.
4. Anonymous. Drospirenone in HRT? *Drug Ther Bull* 2009; 47: 41–4.
5. Mallareddy M, *et al.* Drospirenone, a new progestogen, for postmenopausal women with hypertension. *Drugs Aging* 2007; 24: 453–66.

Premenstrual syndrome. The use of drospirenone with ethinylestradiol has been studied in the management of premenstrual syndrome (p. 2272.3). A systematic review[1] of 5 studies found some evidence that the combination may be useful in the treatment of premenstrual dysphoric disorder. However, it was unknown whether the effect lasted beyond 3 cycles of treatment, whether the combination was effective for less severe symptoms, or whether combinations using drospirenone were any better than combined contraceptives containing other progestogens.

1. Lopez LM, *et al.* Oral contraceptives containing drospirenone for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 16/11/09).

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3. Drospirenone has antimineralocorticoid activity and therefore should not be used in patients at risk of hyperkalaemia, such as those with renal or hepatic impairment or adrenal insufficiency.

Reviews.

1. Heinemann LAJ, Dinger J. Safety of a new oral contraceptive containing drospirenone. *Drug Safety* 2004; 27: 1001–18.
2. Simoncini T, Genazzani AR. A review of the cardiovascular and breast actions of drospirenone in preclinical studies. *Climacteric* 2010; 13: 22–33.

Effects on the cardiovascular system. As with combined oral contraceptives containing other progestogens, there are reports[1-4] of thrombotic and ischaemic events in patients taking a preparation of ethinylestradiol and drospirenone. The extent of risk associated with hormonal contraceptives that contain drospirenone is mentioned under Venous Thromboembolism, p. 2238.1.

1. Vayá A, *et al.* Transient ischaemic attack associated with the new contraceptive Yasmin. *Thromb Res* 2003; 112: 121.
2. van Grootheest K, Vrieling T. Thromboembolism associated with the new contraceptive Yasmin. *BMJ* 2003; 326: 257.
3. Orti G, *et al.* Acute myocardial infarction associated with Yasmin oral contraceptive. *Clin Appl Thromb Hemost* 2007; 13: 336–7.
4. Girolami A, *et al.* Retinal central artery occlusion in a young woman after ten days of a drospirenone-containing oral contraceptive (Yasmin). *Thromb Haemost* 2007; 98: 473–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies drospirenone in combined hormonal contraceptives 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 04/10/11)

Renal impairment. US licensed product information for preparations containing drospirenone contra-indicates its use in renal impairment, and in the UK it is contra-indicated in severe impairment. A study[1] of women with renal impairment that was mild (creatinine clearance 50 to 80 mL/minute) or moderate (30 to 50 mL/min) found a trend toward increasing drospirenone exposure with decreasing creatinine clearance. Serum-potassium concentrations were not significantly altered by drospirenone, despite the concomitant use of other drugs that can also potentially increase potassium concentrations including beta blockers and ACE inhibitors.

1. Schürmann R, *et al.* Effect of drospirenone on serum potassium and drospirenone pharmacokinetics in women with normal or impaired renal function. *J Clin Pharmacol* 2006; 46: 867–75.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3, and Hormone Replacement Therapy, p. 2251.1. Because drospirenone has antimineralocorticoid activity, it may potentially exacerbate the effects of drugs that can increase serum-potassium, such as ACE inhibitors, angiotensin II receptor antagonists, aldosterone antagonists, potassium-sparing diuretics, or NSAIDs. Drospirenone may also reduce blood pressure, such that antihypertensive treatment may require adjustment.

Diuretics. The pharmacokinetics of hydrochlorothiazide were not affected by the addition of drospirenone and estradiol in a placebo-controlled study of 36 hypertensive postmenopausal women.[1] However, those given the combination in this study developed lower blood pressure and higher serum-potassium concentrations, which was attributed to the antimineralocorticoid effect of drospirenone.[2] Nontheless, there were no cases of hyperkalaemia. It has been suggested that these potential antihypertensive and potassium-sparing effects might be beneficial in women requiring treatment for both menopausal symptoms and hypertension (see also Menopausal Disorders, above).

1. Karara AH, *et al.* Pharmacokinetics and pharmacodynamics of drospirenone-estradiol combination hormone therapy product coadministered with hydrochlorothiazide in hypertensive postmenopausal women. *J Clin Pharmacol* 2007; 47: 1292–1302.
2. Preston RA, *et al.* Randomized, placebo-controlled trial of the effects of drospirenone-estradiol on blood pressure and potassium balance in hypertensive postmenopausal women receiving hydrochlorothiazide. *Menopause* 2007; 14: 408–14.

NSAIDs. Drospirenone has the potential to exacerbate the effects of other drugs, such as NSAIDs, that can increase serum potassium. Licensed product information suggests that a clinical effect is unlikely in practice, although the use of several such drugs together or the presence of renal impairment may increase the risk. In a small study[1] of healthy postmenopausal women, there was no evidence that potassium concentrations were any higher when *indometacin* was used with a combination of drospirenone plus estradiol compared with indometacin alone.

1. Schütt B, *et al.* Coadministration of estradiol/drospirenone and indomethacin does not cause hyperkalemia in healthy postmenopausal women: a randomized open-label crossover study. *J Clin Pharmacol* 2007; 47: 774–81.

Pharmacokinetics

After oral doses, drospirenone is rapidly absorbed with a bioavailability of about 76%. It is about 97% bound to plasma proteins, though it does not bind to sex hormone binding globulin or corticosteroid binding globulin. It is extensively metabolised with a terminal half-life of about 30 to 40 hours. The metabolites are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Diva Total.

Multi-ingredient Preparations. *Arg.*: Angeliq; Damsel; Damsella; Diva; Divina; Eos; Equifem; Gadofem; Isis Fe; Isis; Jade; Kala; Kir; Kirum; Kirumelle; Maxima MD 24; Maxima; Umma; Yasmin; Yasminelle; YAZ; *Austral.*: Angeliq; Yasmin; YAZ; *Austria*: Aliane; Angeliq; Yasmin; Yasminelle; YAZ; Yirala; *Belg.*: Angel-

iq; Rimendia; Yasmin; Yasminelle; YAZ; *Braz.*: Angeliq; Elani; Yasmin; YAZ; *Canad.*: Angeliq; Yasmin; YAZ; *Chile*: Altesse; Angeliq; Clinomat; Dahlia; Femelle; Femiplus; Miafem; Vexa; Yasmin; YAZ; *China*: Angeliq (安今益); Yasmin (优思明); *Cz.*: Angeliq; Belanette; Belusha; Daylette; Drosetil; Eloine; Jangee; Kirga; Maitalon; Softinelle; Sylviane; Yadine; Yasminelle; YAZ; *Denm.*: Angemin; Dretine; Eloine; Finminette; Movinella; Palandra; Rubira; Yasmin; Yasminelle; YAZ; *Fin.*: Angeliq; Linatera; Liofora; Palandra; Stefaminelle; Tasminetta; Yasmin; Yasminelle; YAZ; *Fr.*: Angeliq; Belanette; Convuline; Drospibel; Jasmine; Jasminelle; Jasminellecontinu; Rimendia; YAZ; *Ger.*: Aida; Angeliq; Petibelle; Yasmin; Yasminelle; YAZ; *Gr.*: Angeliq; Liofora; Yasmin; Yasminelle; YAZ; *Hong Kong*: Angeliq; Yasmin; YAZ; *Hung.*: Angeliq; Jangee; Symicia; Volina; Yadine; Yasminelle; *India*: Crisanta; Dronis; *Indon.*: Angeliq; Yasmin; YAZ; *Irl.*: Allurene†; Angeliq; Dretine; Dretinelle; Enador; Liofora; Palandra; Yasmin; Yasminelle; YAZ; *Israel*: Angeliq; Yasmin; Yasminelle†; YAZ; *Ital.*: Angeliq; Credigyne; Credigynette; Midiana; Yarina; Yasmin; Yasminelle; YAZ; *Malaysia*: Angeliq; Yasmin; YAZ; *Mex.*: Angeliq; Radiance; Yasmin; *Neth.*: Allurene†; Angeliq; Armarrok; Armunia; Belanette; Liofora; Palandra; Rosal; Vallclara; Volina; Yasmin; Yasminelle; YAZ; Yira†; Yvidually; *Norw.*: Finminette; Rubira; Yasmin; Yasminelle; YAZ; *NZ*: Yasmin; YAZ; *Philipp.*: Angeliq; Yasmin; YAZ; *Pol.*: Aliane; Angeliq; Asubtela; Dronin; Linatera; Midiana; Nataya; Yasmin; Yasminelle; YAZ; *Port.*: Aliane; Allurene; Angeliq; Petibelle; Yasmin; Yasminelle; YAZ; *Rus.*: Angeliq (Анжелик); Yarina (Ярина); YAZ (Джес); *S.Afr.*: Angeliq; Yasmin; YAZ; *Singapore*: Yasmin; YAZ; *Spain*: Angeliq; Antin; Antinelle; Aranka; Arankelle; Daylette; Drelle; Dretine; Dretinelle; Drosiane Diario; Drosianelle; Drospil; Drosure; Drosurelle; Eloine; Liofora; Yasmin; Yasminelle; YAZ; Yira; *Swed.*: Angemin; Eloine; Liofora; Yasmin; Yasminelle; YAZ; *Switz.*: Angeliq; Eloine; Yasmin; Yasminelle; YAZ; *Thai.*: Angeliq; Melodia; Yasmin; YAZ; *Turk.*: Angeliq; Yasmin; Yazz; *UK*: Angeliq; Yasmin; YAZ; *Ukr.*: Angeliq (Анжелик); Darilia (Дарилия); Midiana (Мидиана); Yarina (Ярина); *USA*: Angeliq; Beyaz; Gianvi; Loryna; Ocella; Safyral; Syeda; Vestura; Yasmin; YAZ; Zarah; *Venez.*: Yasmin.

Pharmacopoeial Preparations
USP 36: Drospirenone and Ethinyl Estradiol Tablets.

Drostanolone Propionate *(BANM, rINNM)* ⊗

Compound 32379; Dromostanolone Propionate (USAN); Drostanolone, propionate de; Drostanoloni Propionas; 2α-Methyldihydrotestosterone Propionate; NSC-12198; Propionato de drostanolona; Дростанолона Пропионат.
17β-Hydroxy-2α-methyl-5α-androstan-3-one propionate.
$C_{23}H_{36}O_3$=360.5
CAS — 58-19-5 (drostanolone); 521-12-0 (drostanolone propionate).
UNII — X20UZS7G4O.

Profile

Drostanolone propionate has anabolic and androgenic properties (see Testosterone, p. 2305.1) and has been used in the treatment of advanced malignant neoplasms of the breast in postmenopausal women. It has been subject to abuse in sport.

Dydrogesterone *(BAN, USAN, rINN)*

6-Dehydro-9β,10α-progesterone; 6-Dehydro-*retro*-progesterone; Didrogesteron; Didrogesterona; Dydrogesteron; Dydrogestérone; Dydrogesteroni; Dydrogesteronum; Isopregnenone; NSC-92336; Дидрогестерон.
9β,10α-Pregna-4,6-diene-3,20-dione.
$C_{21}H_{28}O_2$=312.5
CAS — 152-62-5.
ATC — G03DB01.
ATC Vet — QG03DB01.
UNII — 90I02KLE8K.

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

Ph. Eur. 8: (Dydrogesterone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone.

USP 36: (Dydrogesterone). A white to pale yellow crystalline powder. Practically insoluble in water; soluble 1 in 40 of alcohol, 1 in 2 of chloroform, and 1 in 200 of ether.

Uses and Administration

Dydrogesterone is a progestogen structurally related to progesterone (p. 2300.2). It does not have oestrogenic or androgenic properties.

Dydrogesterone has been given orally in the treatment of menstrual disorders such as menorrhagia (p. 2300.3), usually in a dose of 10 mg twice daily in a cyclical regimen, and for the treatment of endometriosis (p. 2264.1) in a dose of 10 mg two or three times daily cyclically or continuously. It has also been given cyclically in doses of 10 mg once or twice daily, or continuously in doses of 5 mg daily, for endometrial protection during menopausal HRT (p. 2244.2).

In threatened miscarriage suggested doses have been 40 mg initially followed by 10 mg or more every 8 hours, continued for a week after symptoms cease then gradually reduced unless symptoms return. In recurrent miscarriage suggested doses have been 10 mg twice daily given cyclically until conception then continuously until week 20 of pregnancy, the dose may then be gradually reduced. However, such use is not recommended unless there is proven progesterone deficiency. Cyclical dydrogesterone has also been used in infertility (p. 2253.1) in doses of 10 mg twice daily.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormone Replacement Therapy, p. 2246.3 and p. 2250.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dydrogesterone 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 04/10/11)

Pregnancy. Anomalies (non-virilising) of the genitourinary tract were found in a 4-month-old baby whose mother had taken dydrogesterone 20 mg daily from the eighth to twentieth week of pregnancy and 10 mg daily from then until term.[1] She had also been given hydroxyprogesterone caproate 250 mg by intramuscular injection weekly from the eighth to the twentieth week.

1. Roberts IF, West RJ. Teratogenesis and maternal progesterone. *Lancet* 1977; ii: 982.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Duphaston†; *Austria*: Duphaston; *Belg.*: Duphaston; *Braz.*: Duphaston; *Chile*: Duphaston; *China*: Duphaston (达芙通); *Cz.*: Duphaston; *Fin.*: Terolut; *Fr.*: Duphaston; *Ger.*: Duphaston; *Gr.*: Duphaston; Medichrol; *Hong Kong*: Duphaston; *Hung.*: Duphaston; *India*: Duphaston; *Indon.*: Duphaston; *Irl.*: Duphaston; *Israel*: Duphaston; *Ital.*: Dufaston; *Malaysia*: Duphaston; *Mex.*: Duphaston; *Neth.*: Duphaston; *NZ*: Duphaston†; *Philipp.*: Duphaston; *Pol.*: Duphaston; *Port.*: Duphaston; *Rus.*: Duphaston (Дюфастон); *S.Afr.*: Duphaston; *Singapore*: Duphaston; *Swed.*: Duphaston†; *Switz.*: Duphaston; *Thai.*: Duphaston; *Turk.*: Duphaston; *Ukr.*: Duphaston (Дуфастон); *Venez.*: Duphaston.

Multi-ingredient Preparations. *Austral.*: Femoston; *Austria*: Femoston Conti; Femoston; *Belg.*: Femoston Conti; Femoston; *Braz.*: Femoston Conti; Femoston; *Chile*: Femoston Conti; Femoston; *China*: Femoston (芬鸣通); *Cz.*: Femoston Conti; Femoston Mini; Femoston; *Fin.*: Femoston Conti; Femoston; *Fr.*: Climaston; Climaston; *Ger.*: Femoston Conti; Femoston; *Gr.*: Femaston; *Hong Kong*: Femoston Conti†; Femoston; *Hung.*: Femoston; *Indon.*: Femoston; *Irl.*: Femoston Conti; Femoston; Femurest-Conti; *Ital.*: Femoston Conti; Femoston; *Malaysia*: Femoston Conti; Femoston; *Mex.*: Lutalmin; *Neth.*: Climaston Continu; Femoston Continu; Femoston; Femphascyl Continu; Femphascyl; *NZ*: Femoston; *Philipp.*: Femoston†; *Pol.*: Femoston Conti; Femoston Mini; Femoston; *Port.*: Femoston 1/5; Femoston; *Rus.*: Femoston (Фемостон); Femoston 1/5 (Фемостон 1/5); *S.Afr.*: Femoston Conti; Femoston; *Singapore*: Femoston Conti; Femoston; *Switz.*: Femoston Conti; Femoston; *Thai.*: Femoston 1/10; Femoston Conti; *Turk.*: Femoston; *UK*: Femapak†; Femoston Conti; Femoston; *Ukr.*: Femoston (Фемостон); *Venez.*: Femoston Conti; Femoston.

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

Elcometrine

Elcometrina; 16-Methylene-17-alpha-acetoxy-19 Norprogesterone; ST-1435.
$C_{23}H_{30}O_4$=370.5
CAS — 7759-35-5.

NOTE. The name Nestorone has been used as a trade mark for elcometrine.

Profile

Elcometrine is a synthetic progestogen that is being developed for use in contraception and menopausal HRT, and in the management of endometriosis.

References.
1. Ylinen K, *et al.* Subdermal progestin implant (Nestorone) in the treatment of endometriosis: clinical response to various doses. *Acta Obstet Gynecol Scand* 2003; 82: 167–72.
2. Sitruk-Ware R, *et al.* Nestorone: clinical applications for contraception and HRT. *Steroids* 2003; 68: 907–13.
3. Sivin I, *et al.* Two-year performance of a Nestorone-releasing contraceptive implant: a three-center study of 300 women. *Contraception* 2004; 69: 137–44.
4. Sivin I, *et al.* Contraceptive vaginal rings releasing Nestorone and ethinylestradiol: a 1-year dose-finding trial. *Contraception* 2005; 71: 122–9.
5. Fraser IS, *et al.* Serum Nestorone and ethinyl estradiol levels, and ovulation inhibition in women using three different dosage combinations of a Nestorone progestogen-ethinyl estradiol contraceptive vaginal ring on a bleeding-signaled regimen. *Contraception* 2005; 72: 40–5.
6. Weisberg E, *et al.* Clinical performance and menstrual bleeding patterns with three dosage combinations of a Nestorone progestogen/ethinyl estradiol contraceptive vaginal ring used on a bleeding-signaled regimen. *Contraception* 2005; 72: 46–52.
7. Croxatto HB, *et al.* Feasibility study of Nestorone-ethinylestradiol vaginal contraceptive ring for emergency contraception. *Contraception* 2006; 73: 46–52.
8. Mahabadi V, *et al.* Combined transdermal testosterone gel and the progestin nestorone suppresses serum gonadotropins in men. *J Clin Endocrinol Metab* 2009; 94: 2313–20.

Epimestrol *(BAN, USAN, rINN)*

Epimestrol; Epimestroli; Epimestrolum; NSC-55975; Org-817; Эпиместрол.
3-Methoxyestra-1,3,5(10)-triene-16α,17α-diol.
$C_{19}H_{26}O_3$=302.4
CAS — 7004-98-0.
ATC — G03GB03.
ATC Vet — QG03GB03.
UNII — 7NE3SDZ38.

Profile

Epimestrol is the 3-methyl ether of the naturally occurring hormone 17-epioestriol. It has been used in the treatment of female infertility due to anovulation and amenorrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Stimovul.

Equilin

Equilina.
3-Hydroxyestra-1,3,5(10),7-tetraen-17-one.
$C_{18}H_{20}O_2$=268.4
CAS — 474-86-2.
UNII — 08O86EX0J4.

Pharmacopoeias. In *US*.

USP 36: (Equilin). Store in airtight containers. Protect from light.

Profile

Equilin is a natural oestrogenic hormone found in horses. Sodium equilin sulfate is one of the components of both conjugated oestrogens (p. 2260.1) and esterified oestrogens (see below) used for menopausal HRT.

Esterified Oestrogens

Esterified Estrogens; Estrógenos esterificados; Эстрогены Этерифицированные.

Pharmacopoeias. In *US*.

USP 36: (Esterified Estrogens). A mixture of the sodium salts of the sulfate esters of the oestrogenic substances, mainly estrone. It contains 75 to 85% of sodium estrone sulfate and 6 to 15% of sodium equilin sulfate, in such a proportion that the total of these two components is not less than 90%, of the labelled amount of esterified oestrogens. A white or buff-coloured amorphous powder; odourless or having a slight characteristic odour. Store in airtight containers.

Profile

Esterified oestrogens have actions and uses similar to those described for estradiol (see p. 2271.1). They are used for the same purposes (mainly menopausal HRT), and in a similar oral dosage, as conjugated oestrogens (see p. 2260.2), although higher cyclical doses of 2.5 to 7.5 mg daily are still licensed for use in female hypogonadism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Menest; *Canad.*: Estragyn; *Chile*: Femibel†; *USA*: Estratab; Menest.

Multi-ingredient Preparations. *Chile:* Delitan; Feminova-T†; *USA:* Covaryx; Estratest†; Syntest.

Pharmacopoeial Preparations
USP 36: Esterified Estrogens Tablets.

Estradiol *(BAN, rINN)*

Beta-oestradiol; Dihidrofoliculina; Dihidroxiestratrieno; Dihidroxiestrina; Dihydrofolliculin; Dihydrotheelin; Dihydroxyoestrin; Estradiolis; Estradiolis; Estradiolum; NSC-9895; Oestradiol; Östradiol; Ösztradiol; Эстрадиол.
Estra-1,3,5(10)-triene-3,17β-diol.
$C_{18}H_{24}O_2$=272.4
CAS — 50-28-2 (anhydrous estradiol); 35380-71-3 (estradiol hemihydrate).
ATC — G03CA03.
ATC Vet — QG03CA03.
UNII — 4TI98Z838E (estradiol); CXY7B3Q98Z (estradiol hemihydrate).

NOTE. In *Martindale* the term oestradiol is used for the endogenous substance.

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

Eur. (see p. vii) includes the hemihydrate.

Ph. Eur. 8: (Estradiol Hemihydrate). A white or almost white crystalline powder or colourless crystals. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; slightly soluble in dichloromethane.

USP 36: (Estradiol). White or creamy-white, odourless, hygroscopic small crystals or crystalline powder. Practically insoluble in water; soluble 1 in 28 of alcohol, 1 in 435 of chloroform, and 1 in 150 of ether; soluble in acetone, in dioxan, and in solutions of fixed alkali hydroxides; sparingly soluble in vegetable oils. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Estradiol Acetate *(BANM, USAN, rINNM)*

Acetato de estradiol; E-3A; Estradiol, Acétate d'; Estradiol-3-acetate; Estradioli Acetas; Oestradiol Acetate; Эстрадиола Ацетат.
Estra-1,3,5(10)-triene-3,17β-diol 3-acetate.
$C_{20}H_{26}O_3$=314.4
CAS — 4245-41-4.
ATC — G03CA03.
ATC Vet — QG03CA03.
UNII — 5R97F5H93P.

Estradiol Benzoate *(BANM, rINN)*

Benzoato de estradiol; Beta-oestradiol Benzoate; Dihydroxyoestrin Monobenzoate; Estradiol, Benzoate d'; Estradiol, benzoato de; Estradiolbensoat; Estradiolbenzoat; Estradiol-benzoát; Estradioli Benzoas; Estradiolibentsoaatti; Estradiolio benzoatas; Estradiolu benzoesan; NSC-9566; Oestradiol Benzoate; Östradiol Benzoat; Ösztradiol-benzoát; Эстрадиола Бензоат.
Estra-1,3,5(10)-triene-3,17β-diol 3-benzoate.
$C_{25}H_{28}O_3$=376.5
CAS — 50-50-0.
ATC — G03CA03.
ATC Vet — QG03CA03.
UNII — 1S4CJB5ZGN.

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

Ph. Eur. 8: (Estradiol Benzoate). An almost white crystalline powder or colourless crystals. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in acetone; freely soluble in dichloromethane; slightly soluble in methyl alcohol.

USP 36: (Estradiol Benzoate). A white to off-white, crystalline powder. Insoluble in water; soluble in alcohol and in acetone; slightly soluble in ether. Store in airtight containers. Protect from light.

Estradiol Cipionate *(BANM, rINNM)*

Cipionato de estradiol; Estradiol, Cipionate d'; Estradiol, cipionato de; Estradiol Cypionate; Estradioli Cipionas; Oestradiol Cyclopentylpropionate; Oestradiol Cypionate; Эстрадиола Ципионат.
Estra-1,3,5(10)-triene-3,17β-diol 17-(3-cyclopentylpropionate).
$C_{26}H_{36}O_3$=396.6
CAS — 313-06-4.
ATC — G03CA03.
ATC Vet — QG03CA03.
UNII — 7E1DV054LO.

Pharmacopoeias. In *US.*

USP 36: (Estradiol Cypionate). A white to practically white crystalline powder, odourless or has a slight odour. Insoluble in water; soluble 1 in 40 of alcohol, 1 in 7 of chloroform, and 1 in 2800 of ether; soluble in acetone and in dioxan; sparingly soluble in vegetable oils. Store in airtight containers. Protect from light.

Estradiol Dipropionate *(BANM, rINNM)*

Dihydroxyoestrin Dipropionate; Dipropionato de estradiol; Estradiol, Dipropionate d'; Estradiol, dipropionato de; Estradioli Dipropionas; Oestradiol Dipropionate; Эстрадиола Дипропионат.
Estra-1,3,5(10)-triene-3,17β-diol dipropionate.
$C_{24}H_{32}O_4$=384.5
CAS — 113-38-2.
ATC — G03CA03.
ATC Vet — QG03CA03.
UNII — NIG5418BXB.

Estradiol Enantate *(BANM, rINNM)*

Enantato de estradiol; Estradiol, Enantate d'; Estradiol, enantato de; Estradiol Enanthate (USAN); Estradioli Enantas; Oestradiol Enanthate; Oestradiol 17-Heptanoate; SQ-16150; Эстрадиола Энантат.
Estra-1,3,5(10)-triene-3,17β-diol 17-heptanoate.
$C_{25}H_{36}O_3$=384.6
CAS — 4956-37-0.
ATC — G03CA03.
ATC Vet — QG03CA03.
UNII — PAP315WZIA.

Estradiol Hexahydrobenzoate *(BANM, rINNM)*

Estradiol, hexahidrobenzoato de; Estradiol, Hexahydrobenzoate d'; Estradioli Hexahydrobenzoas; Hexahidrobenzoato de estradiol; Oestradiol Hexahydrobenzoate; Эстрадиола Гексагидробензоат.
Estra-1,3,5(10)-triene-3,17β-diol 17-cyclohexanecarboxylate.
$C_{25}H_{34}O_3$=382.5
CAS — 15140-27-9.
ATC — G03CA03.
ATC Vet — QG03CA03.

Estradiol Phenylpropionate *(BANM, rINNM)*

Estradiol, fenilpropionato de; Estradiol, Phénylpropionate de; Estradioli Phenylpropionas; Fenilpropionato de estradiol; Oestradiol Phenylpropionate; Östradiol Fenilpropiyonat; Эстрадиола Фенилпропионат.
Estra-1,3,5(10)-triene-3,17β-diol 17-(3-phenylpropionate).
$C_{27}H_{32}O_3$=404.6
ATC — G03CA03.
ATC Vet — QG03CA03.

Estradiol Valerate *(BANM, rINN)*

Estradiol, valérate d'; Estradiol, valerato de; Estradioli Valeras; Estradiolio valeratas; Estradiolivaleraatti; Estradiolvalerat; Estradiol-valerát; NSC-17590; Oestradiol Valerate; Östradiol-17-Valerat; Ösztradiol-valerát; Valerato de estradiol; Эстрадиола Валерат.
Estra-1,3,5(10)-triene-3,17β-diol 17-valerate.
$C_{23}H_{32}O_3$=356.5
CAS — 979-32-8.
ATC — G03CA03.
ATC Vet — QG03CA03.
UNII — OKG364O896.

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

Ph. Eur. 8: (Estradiol Valerate). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; soluble in alcohol. Protect from light.

USP 36: (Estradiol Valerate). A white crystalline powder which is usually odourless or may have a faint fatty odour. Practically insoluble in water; soluble in benzyl benzoate, in dioxan, in methyl alcohol, and in castor oil; sparingly soluble in arachis oil and in sesame oil. Store in airtight containers. Protect from light.

Uses and Administration

Estradiol is the most active of the naturally occurring oestrogens (for further details, see p. 2231.1). Estradiol and its semisynthetic esters and other natural oestrogens are mainly used as menopausal HRT (see p. 2244.2) whereas synthetic derivatives such as ethinylestradiol have a major role as components of combined hormonal contraceptives (see p. 2231.3). Estradiol may also be used as replacement therapy for female hypogonadism or primary ovarian failure (p. 2252.3). Replacement therapy ('add-back' therapy) may also be given to women in whom the pituitary-ovarian axis is suppressed by therapy with gonadorelin or its analogues.

Estradiol hemihydrate 1.03 mg is equivalent to about 1 mg of the anhydrous substance.

For **menopausal HRT** oral preparations or transdermal patches of estradiol are commonly used. Other transdermal formulations, subcutaneous implants, and a nasal spray are also available. Intramuscular injections were formerly used. In women with a uterus, a progestogen is also required, given cyclically or continuously, usually orally although some combined transdermal preparations are available. Local vaginal estradiol preparations are used specifically for the treatment of menopausal atrophic vaginitis; these are generally recommended for short-term use only, if given without a progestogen in women with a uterus, although specific recommendations vary between products.

For *oral* use estradiol or estradiol valerate is normally given in doses of 1 or 2 mg daily cyclically, or more often continuously. Estradiol acetate may be given in an initial dose of 450 micrograms daily, increasing if necessary to 0.9 or 1.8 mg once daily.

Estradiol may be used topically as *transdermal skin patches* to provide a systemic effect; a variety of patches are available which release between 25 and 100 micrograms of estradiol every 24 hours. A low-dose patch supplying 14 micrograms daily is also available specifically for the prevention of postmenopausal osteoporosis in women at significant risk; with this low dose, the addition of a 14-day course of progestogen in women with a uterus is only required once every 6 to 12 months. Depending on the preparation, patches are replaced once or twice weekly. Each new patch is applied to a different area of skin in rotation, usually below the waistline; patches should not be applied on or near the breasts. *Topical gel* preparations are also used for systemic effect. The usual applied dose is 0.25 to 1.5 mg of estradiol daily, depending on the preparation, but up to 3 mg daily may be required for control of menopausal symptoms in some women. The gel should not be applied on the face or on or near the breasts, vagina, or vulval region. A *topical emulsion* is also available; estradiol hemihydrate 8.7 mg is applied daily to provide a systemic estradiol dose of about 50 micrograms. A *transdermal spray* has also been developed, delivering a single dose of estradiol 1.53 mg onto the skin. It should be applied to the skin of the inner surface of the forearm, and the dose may be increased up to 3 sprays once daily in the morning, at separate sites on the forearm, according to response.

A *nasal spray* is available, delivering 150 micrograms of estradiol hemihydrate per spray. The usual initial dose is 150 micrograms daily (1 spray in 1 nostril). After 2 or 3 cycles the dose may be adjusted according to response; the usual maintenance dose is 300 micrograms daily (1 spray in each nostril once daily) but may range from 150 micrograms once daily up to 450 to 600 micrograms daily in 2 divided doses.

In order to prolong the duration of action *subcutaneous implants* of estradiol may be used. The dose of estradiol is generally 25 to 100 mg with a new implant being given after about 4 to 8 months according to oestrogen concentrations.

Estradiol may be used locally:

- a 10-microgram *vaginal tablet* is inserted in an initial dose of one tablet daily for 2 weeks, followed by a maintenance dose of one tablet twice a week
- alternatively, a 0.01% *vaginal cream* is inserted in initial amounts of 2 to 4 g of cream daily for 1 to 2 weeks then gradually reduced to half the initial dose for a similar period, followed by a maintenance dose of 1 g up to 3 times weekly
- a local delivery system using a 3-month *vaginal ring* contains 2 mg of estradiol hemihydrate, and delivers about 7.5 micrograms of estradiol per 24 hours. Another 3-month vaginal ring system, which contains estradiol acetate, releases either 50 or 100 micrograms of estradiol daily, and is used for the relief of both local and systemic postmenopausal symptoms.

Intramuscular injections of estradiol benzoate or valerate esters have been used as oily depot solutions, usually given once every 3 to 4 weeks. The cipionate, dipropionate, enantate, hexahydrobenzoate, phenylpropionate, and undecylate esters have been used similarly.

Estradiol valerate is used as the oestrogenic component in some combined oral **contraceptives.** Doses ranging from 1 to 3 mg daily are used in multiphasic preparations. The enantate, cipionate, benzoate butyrate, and valerate esters are used in combined injectable contraceptives.

Estradiol and other oestrogens have sometimes been used in higher doses for palliative treatment in **prostate cancer** (p. 712.3) and **breast cancer** in men and postmenopausal women (p. 702.1).

Administration. BUCCAL AND SUBLINGUAL ADMINISTRATION. Estradiol is absorbed through the *buccal* route, and has been reported to improve postmenopausal vasomotor symptoms.[1] A pharmacokinetic study[2] of micronised estradiol found the *sublingual* route resulted in more rapid

absorption, a higher peak concentration, and more rapid elimination, than oral dosage. Sublingual micronised estradiol has been studied for the management of postpartum depression.[3]

1. Gass MS, *et al.* A short study in the treatment of hot flashes with buccal administration of 17-β estradiol. *Maturitas* 2004; 49: 140–7.
2. Price TM, *et al.* Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 β-estradiol. *Obstet Gynecol* 1997; 89: 340–5.
3. Ahokas A, *et al.* Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17 β-estradiol: a preliminary study. *J Clin Psychiatry* 2001; 62: 332–6.

IMPLANTS. There may be a striking interpatient variation in blood-estradiol concentrations in women receiving estradiol implants,[1] and symptoms of oestrogen deficiency have re-appeared in some patients even though serum-estradiol concentrations were within or above the physiological range.[2] After debate on the appropriateness of using serum concentrations of estradiol as a guide to implant use, rather than symptoms,[3-7] it is now recommended that estradiol concentration should be monitored during therapy.

Cyclical progestogen may be required for a prolonged period after removal of estradiol implants in women with a uterus.[7]

1. Guirgis RR. Oestradiol implants: what dose, how often? *Lancet* 1987; ii: 856.
2. Gangar K, *et al.* Symptoms of oestrogen deficiency associated with supraphysiological plasma oestradiol concentrations in women with oestradiol implants. *BMJ* 1989; 299: 601–2.
3. Ginsburg J, Hardiman P. Oestrogen deficiency and oestradiol implants. *BMJ* 1989; 299: 1031.
4. Studd J, *et al.* Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; 299: 1400–1.
5. Swyer GIM. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; 299: 854.
6. Tobias JH, Chambers TJ. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; 299: 854.
7. Wardle P, Fox R. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; 299: 1102.

INTRANASAL ADMINISTRATION. The intranasal route for estradiol HRT has been reviewed.[1] It appears to be comparable in efficacy to oral[2] or transdermal use[3,4] in the treatment of menopausal symptoms. As with transdermal application, the intranasal route avoids intestinal and hepatic first-pass metabolism.

1. Dooley M, *et al.* Estradiol-intranasal: a review of its use in the management of menopause. *Drugs* 2001; 61: 2243–62.
2. Studd J, *et al.* Efficacy and acceptability of intranasal 17 β-oestradiol for menopausal symptoms: randomised dose-response study. *Lancet* 1999; 353: 1574–8. Correction. *ibid.*; 354: 780.
3. Lopes P, *et al.* Randomized comparison of intranasal and transdermal estradiol. *Obstet Gynecol* 2000; 96: 906–12.
4. Davis SR, *et al.* Intranasal versus transdermal matrix oestrogen replacement in Australasian women. *Maturitas* 2005; 51: 163–71.

TRANSDERMAL ADMINISTRATION. Transdermal estradiol given via *patches* applied to the skin has been reviewed.[1-3] This method of delivery has certain advantages over the oral route in that gastrointestinal and hepatic first-pass metabolism is avoided, liver enzymes are not stimulated (although this may also mean that beneficial effects on serum lipids are absent), and the prolonged drug release from the patch means less frequent application is necessary and hence patient compliance may be improved. For oestrogen replacement in menopausal and postmenopausal women estradiol patches are used continuously or in a cyclical manner, with added progestogen for part of the cycle in those women with an intact uterus. This does not lead to drug accumulation and produces blood-estradiol concentrations and estradiol to estrone ratios similar to those normally seen in premenopausal women. The patch is well tolerated with skin irritation being the main problem. Patches are as effective as oral oestrogens in treating menopausal and postmenopausal symptoms such as flushing and vaginal atrophy and in preventing osteoporosis. Combined HRT patches, providing both estradiol and a progestogen, have also been developed.[4]

Estradiol is also effective when applied topically to the skin as a *gel*[5] or *emulsion*.[6]

1. Balfour JA, Heel RC. Transdermal estradiol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of menopausal complaints. *Drugs* 1990; 40: 561–82.
2. Cheang A, *et al.* A risk-benefit appraisal of transdermal estradiol therapy. *Drug Safety* 1993; 9: 365–79.
3. Jewelewicz R. New developments in topical estrogen therapy. *Fertil Steril* 1997; 67: 1–12.
4. Dando TM, Perry CM. 17 β-Estradiol/levonorgestrel transdermal system. *Treat Endocrinol* 2004; 3: 319–24.
5. Naunton M, *et al.* Estradiol gel: review of the pharmacology, pharmacokinetics, efficacy, and safety in menopausal women. *Menopause* 2006; 13: 517–27.
6. Simon JA. ESTRASORB Study Group. Estradiol in micellar nanoparticles: the efficacy and safety of a novel transdermal drug-delivery technology in the management of moderate to severe vasomotor symptoms. *Menopause* 2006; 13: 222–31.

Depression. The use of oestrogen therapy in the treatment of premenopausal women with postnatal depression was reported to be effective in a few studies.[1,2] However, although such therapy might be a useful adjunct to conventional treatment (see Depression, p. 398.1), the risk of serious adverse effects including thrombosis may limit its value.

Whether oestrogens are of benefit in older women, typically with depression associated with the menopause (p. 2245.1), is less clear. Some studies of transdermal estradiol have reported benefit,[3-5] whereas other studies of transdermal[6] or oral[7] dosage have not found it to be effective. Whether the presence of a progestogen in combination HRT would reduce any purported benefit is also unclear. Antidepressants remain the standard of care in perimenopausal or postmenopausal women with clinical depression.

1. Gregoire AJP, *et al.* Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996; 347: 930–3.
2. Ahokas A, *et al.* Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17 β-estradiol: a preliminary study. *J Clin Psychiatry* 2001; 62: 332–6.
3. Soares C de N, *et al.* Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women. *Arch Gen Psychiatry* 2001; 58: 529–34.
4. Cohen LS, *et al.* Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *Am J Psychiatry* 2003; 160: 1519–22.
5. Schiff R, *et al.* Short-term transdermal estradiol therapy, cognition and depressive symptoms in healthy older women: a randomised placebo controlled pilot cross-over study. *Psychoneuroendocrinology* 2005; 30: 309–15.
6. Morrison MF, *et al.* Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 2004; 55: 406–12.
7. Almeida OP, *et al.* A 20-week randomized controlled trial of estradiol replacement therapy for women aged 70 years and older: effect on mood, cognition and quality of life. *Neurobiol Aging* 2006; 27: 141–9.

Gender reassignment. Oestrogens are used in male-to-female transsexuals to develop and maintain secondary sexual characteristics. Although ethinylestradiol and conjugated oestrogens have been used for this purpose, and there is some evidence that such use can improve vascular function,[1] others consider ethinylestradiol too thrombogenic at the doses required [typically 50 to 100 micrograms daily or more] and suggest that estradiol, as the valerate in oral doses of 2 to 4 mg daily, or transdermally as a patch supplying 100 micrograms daily, is the oestrogen of choice.[2,3] Cyproterone acetate is usually also given for its anti-androgenic effect (see p. 2261.3).

1. New G, *et al.* Long-term estrogen therapy improves vascular function in male to female transsexuals. *J Am Coll Cardiol* 1997; 29: 1437–44.
2. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; 64 (suppl 2): 31–6.
3. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; 93: 19–25.

Growth disorders. Supraphysiological doses of oestrogens inhibit somatic growth and have been used, with a cyclical progestogen, to reduce final height in girls with constitutional tall stature, although such treatment has declined markedly with changing social norms.[1] In early reports, diethylstilbestrol was used, but this is an unsuitable choice because of the increased risk of cancer. Ethinylestradiol has been given in the past in doses of up to 500 micrograms daily, but doses of 50 to 100 micrograms daily came to be preferred, although lower doses may be equally effective.[2,3] Conjugated oestrogens have also been used, and a study[4] reported that doses of 7.5 to 11.25 mg daily resulted in an average decrease of about 5 cm from final predicted height. In practice, doses as low as 625 micrograms daily have been used.[3] Reported height reductions have ranged from 2 to 10 cm but studies are difficult to compare. Treatment has generally been continued until closure of the epiphyses, but the effects of oestrogen therapy may be influenced by both chronological and bone age at the onset of treatment, duration of treatment, the oestrogen used and its dose, and the point of final height assessment.[2] High-dose oestrogen therapy is also associated with adverse effects such as weight gain, headache, nausea, and pigmentation of the areolae or nipples,[2,3] and there can be adverse changes to haemostatic and lipid measures.[2] A retrospective cohort review[5] has also reported that girls who had been treated with high-dose oestrogens were more likely to report fertility problems in later life than similar girls who had not been treated.

Oestrogen therapy has occasionally been used to help promote growth in girls with constitutional delayed puberty (see p. 2252.1).

1. Lee JM, Howell JD. Tall girls: the social shaping of a medical therapy. *Arch Pediatr Adolesc Med* 2006; 160: 1035–9.
2. Drop SLS, *et al.* Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 1998; 19: 540–58.
3. Barnard ND, *et al.* The current use of estrogens for growth-suppressant therapy in adolescent girls. *J Pediatr Adolesc Gynecol* 2002; 15: 23–6.
4. Weimann E, *et al.* Oestrogen treatment of constitutional tall stature: a risk-benefit ratio. *Arch Dis Child* 1998; 78: 148–51.
5. Venn A, *et al.* Oestrogen treatment to reduce the adult height of tall girls: long-term effects on fertility. *Lancet* 2004; 364: 1513–18.

Haemorrhagic disorders. Limited evidence supports the use of oestrogens in various bleeding disorders. There have been mixed results from small studies of oestrogens, given alone or with a progestogen, in patients with hereditary haemorrhagic telangiectasia;[1,2] the use of a combined oral contraceptive has been suggested as a suitable option for fertile women with symptomatic epistaxis.[3] There are also some reports[2,4,5] of bleeding being reduced in patients with gastrointestinal vascular malformations from other causes. Conjugated oestrogens have been used in haemorrhagic disorders associated with chronic renal failure and haemorrhagic cystitis (see p. 2260.3).

1. Vase P. Estrogen treatment of hereditary hemorrhagic telangiectasia. *Acta Med Scand* 1981; 209: 393–6.
2. van Cutsem E, *et al.* Treatment of bleeding gastrointestinal vascular malformations with oestrogen-progesterone. *Lancet* 1990; 335: 953–5.
3. Jameson JJ, Cave DR. Hormonal and antihormonal therapy for epistaxis in hereditary hemorrhagic telangiectasia. *Laryngoscope* 2004; 114: 705–9.
4. Bronner MH, *et al.* Estrogen-progesterone therapy for bleeding gastrointestinal telangiectasias in chronic renal failure: an uncontrolled trial. *Ann Intern Med* 1986; 105: 371–4.
5. Siple JP, *et al.* Use of estrogen therapy in a patient with gastrointestinal bleeding secondary to arteriovenous malformations. *Ann Pharmacother* 1997; 31: 1311–14.

Lactation inhibition. Synthetic oestrogens (e.g. quinestrol) and nonsteroidal oestrogens (e.g. diethylstilbestrol) were historically used to suppress lactation (p. 2130.1). However, this use is now considered inappropriate because of an increased risk of puerperal thromboembolism.

Premenstrual syndrome. Premenstrual syndrome (PMS) presents as a variable combination of psychological and somatic symptoms occurring during the luteal phase of the menstrual cycle, which resolve during, and immediately after, menstruation. Another term, premenstrual dysphoric disorder, has been proposed to cover severe cyclical mood disorder that is functionally incapacitating.[1,2] Whereas about 20 to 40% of women have complaints that may be classified as PMS, only 3 to 8% meet criteria for premenstrual dysphoric disorder.[2] The term premenstrual tension (PMT) has sometimes been applied to the psychological symptoms. Many symptoms of PMS are the same as normal premenstrual symptoms, but are more severe. The aetiology of PMS is not fully understood, although it is thought that affected women may be more sensitive to the effects of normal hormonal fluctuations on CNS neurotransmitter function.[2]

Initial management includes non-medical interventions[3] such as education and support, counselling, stress management, relaxation techniques, and exercise; caffeine and salt restriction are of unproven benefit. The herbal remedy agnus castus has been found to be of benefit.[4] For patients with moderate to severe symptoms, several drugs have been tried with varying degrees of success; objective assessment of efficacy has been hampered by varying diagnostic criteria, a marked placebo response, and difficulties in obtaining reproducible responses. Treatment may be aimed at modifying the menstrual cycle or treating specific symptoms.

SSRIs, particularly fluoxetine and sertraline, have been shown in controlled studies to alleviate both psychological and somatic symptoms in women with PMS.[3,5,6] They may be given intermittently (only in the luteal phase) or continuously for severe PMS,[1,3] and some suggest that they are particularly useful when mood symptoms predominate.[1,7] If treatment with one SSRI is ineffective or not tolerated, another SSRI or *venlafaxine* may be substituted.[1,3,5] There is limited information on the use of SSRIs for PMS in adolescents, and precautions regarding suicidal ideation in young adults should be considered.[2] *Clomipramine*, a nonselective serotonin reuptake inhibitor, has been tried for PMS with some success. The anxiolytic *alprazolam* has also been used, and may be useful when insomnia or overwhelming anxiety are significant.[7] However, use of this and other benzodiazepines should be restricted to the luteal phase of the cycle in selected patients to minimise the risk of dependence and tolerance.[8]

Abdominal bloating and swelling associated with PMS has traditionally been thought to be due to sodium and water retention. However, in most women with these symptoms there is no evidence of an increase in bodyweight or in body sodium or total water, and use of *diuretics* is therefore not justified.[9] Nevertheless, in women with appreciable weight gain and abdominal bloating in the luteal phase, the aldosterone antagonist spironolactone may be useful.[1,5,10] Another symptom of PMS, cyclical mastalgia, is discussed on p. 2265.1.

Pyridoxine has been tried on the basis that it is a cofactor in neurotransmitter (specifically serotonin) synthesis, and has been found to relieve depression induced by oral contraceptives in selected patients. However, its efficacy in PMS is equivocal, and high daily doses have been associated with neurotoxicity.[11] *Calcium* supplementation may relieve symptoms of PMS.[3,12]

Treatments that modify the menstrual cycle have often been used in women with PMS. In general, drugs with proven efficacy such as danazol, oestrogen implants, and gonadorelin analogues are reserved for women with severe PMS unresponsive to other treatments, because of their adverse effects. *Progestogen* therapy was once popular, but

beneficial responses have not been universally achieved and the theory that progesterone was necessary to correct a hormone imbalance is now losing ground. In addition, a systematic review[13] of clinical studies found no evidence to support the use of progesterone or progestogens for PMS. *Combined oral contraceptives* have met with limited success.[2] They may be useful in some women for the control of somatic symptoms, but in others, PMS is caused or exacerbated by them. There is some suggestion that combined contraceptives containing drospirenone may be more effective in managing PMS than those containing progestogens such as levonorgestrel or norethisterone.[3] Regimens that have a shorter tablet-free interval (less than 7 days) may be useful for some women,[7] and consideration should be given to continuous rather than cyclical use.[3] Perimenopausal women may benefit from *oestrogen* delivered from transdermal patches. In women with a uterus, use with a cyclical progestogen is required to avoid endometrial hyperplasia; unfortunately, the progestogen may be associated with the return of symptoms. Possible strategies to minimise this include the use of a less androgenic progestogen, reducing the frequency with which it is given, or using an intra-uterine device to deliver the progestogen locally.[14] *Danazol* can be useful,[1,3] but there is concern over its adverse effects on lipids during long-term use and over the risk of masculinisation of a female fetus should pregnancy occur. For patients with severe symptoms not amenable to other treatments, gonadorelin analogues such as *goserelin* can be used to eliminate ovarian function, 'add-back' treatment with oestrogen plus progestogen being given to protect against the adverse effects of oestrogen deficiency including osteoporosis.[3] This treatment is very effective for both physical and psychological symptoms.[15] Short-term use (3 months) of a gonadorelin analogue alone has been used to confirm the diagnosis of PMS, or to predict the response to bilateral oophorectomy.[1,3]

1. Johnson SR. Premenstrual syndrome, premenstrual dysphoric disorder, and beyond: a clinical primer for practitioners. *Obstet Gynecol* 2004; 104: 845–59.
2. Braverman PK. Premenstrual syndrome and premenstrual dysphoric disorder. *J Pediatr Adolesc Gynecol* 2007; 20: 3–12.
3. Royal College of Obstetricians and Gynaecologists. Management of premenstrual syndrome (Green-top guideline 48, issued December 2007). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT48ManagementPremenstrualSyndrome.pdf (accessed 24/11/09)
4. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001; 322: 134–7.
5. Halbreich U. Algorithm for treatment of premenstrual syndromes (PMS): experts' recommendations and limitations. *Gynecol Endocrinol* 2005; 20: 48–56.
6. Brown J, *et al.* Selective serotonin reuptake inhibitors for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 24/11/09).
7. Yonkers KA, *et al.* Premenstrual syndrome. *Lancet* 2008; 371: 1200–10.
8. Severino SK, Moline ML. Premenstrual syndrome: identification and management. *Drugs* 1995; 49: 71–82.
9. O'Brien PMS. Helping women with premenstrual syndrome. *BMJ* 1993; 307: 1471–5.
10. Mortola JF. A risk-benefit appraisal of drugs used in the management of premenstrual syndrome. *Drug Safety* 1994; 10: 160–9.
11. Wyatt KM, *et al.* Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ* 1999; 318: 1375–81.
12. 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.
13. Wyatt K, *et al.* Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; 323: 776–80.
14. Hassan I, *et al.* PMS in the perimenopause. *J Br Menopause Soc* 2004; 10: 151–6.
15. Wyatt KM, *et al.* The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis. *BJOG* 2004; 111: 585–93.

Turner's syndrome. Oestrogen therapy is used in Turner's syndrome (p. 2254.3) to produce sexual maturation and the development of secondary sexual characteristics, as well as to avoid complications such as osteoporosis. Low-dose oestrogen therapy may be started at about one-tenth to one-eighth of the adult replacement dose if spontaneous puberty has not begun by 12 to 13 years of age. Estradiol has been given in initial doses of 200 to 400 micrograms each month as an intramuscular depot injection, or 250 micrograms orally daily. Transdermal estradiol patches have also been tried, with the intention of giving an initial dose of 6.25 micrograms daily. However, because commercially available patches deliver 14 or 25 micrograms daily, methods of dose fractionation have included using a quarter of a patch overnight or daily, or using a whole patch for 7 to 10 days per month. It is unknown whether such methods deliver equivalent doses.[1] The use of transdermal estradiol gel has also been studied, starting with a dose of 100 micrograms daily.[2]

The oestrogen dose is gradually increased to adult doses over 2 to 4 years, to promote a normal pace of pubertal development. A cyclic progestogen is usually added about 2 years after starting oestrogen therapy or when breakthrough bleeding occurs. There is no consensus on which oestrogen is preferred, but transdermal or injectable depot estradiol may be the most physiological options. Adult daily doses of estradiol are generally 100 to 200 micrograms transdermally or 2 to 4 mg orally, or a monthly dose of injectable estradiol cipionate 2.5 mg may be used. Alternative oestrogens include oral ethinylestradiol 20 micrograms, or conjugated oestrogens 1.25 to 2.5 mg, daily. Progesterone may be given in oral doses of 200 mg daily on days 20 to 30 of a monthly cycle, or days 100 to 120 of a 3-month cycle. A combined oral contraceptive is another option for maintenance.[1]

1. Bondy CA. The Turner Syndrome Consensus Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007; 92: 10–25.
2. Filippo S, *et al.* Use of percutaneous estrogen gel for induction of puberty in girls with Turner syndrome. *J Clin Endocrinol Metab* 2004; 89: 3241–7.

Adverse Effects

The adverse effects of estradiol and other oestrogens are related, in part, to dose and duration of therapy, and to the gender and age of the recipient. In addition, adverse effects may be modified by a progestogen in combined oral contraceptives or menopausal HRT. Whether adverse effects of natural and synthetic oestrogens differ, and whether the dosage route has an effect, is less clear.

The adverse effects of oestrogens used in hormonal contraceptives are considered in detail starting on p. 2233.3. Those of oestrogens used in HRT are considered in detail starting on p. 2246.3.

The use of oestrogens in children may cause premature closure of the epiphyses resulting in decreased final adult height.

Large doses of oestrogens used in palliation of cancers have also been associated with nausea, fluid retention, venous and arterial thrombosis, and cholestatic jaundice. In men, they cause impotence and feminising effects such as gynaecomastia. In women, they may cause withdrawal bleeding, and, when used for breast cancer, they have caused hypercalcaemia and bone pain.

Effects on the skin. Transdermal patches in which estradiol is dissolved in the adhesive matrix may cause fewer skin reactions than those releasing estradiol from an alcoholic reservoir.

1. Ross D. Randomised crossover comparison of skin irritation with two transdermal oestradiol patches. *BMJ* 1997; 315: 288.

Precautions

The precautions for the use of estradiol and other oestrogens used as menopausal HRT are considered in detail starting on p. 2250.1. Those for oestrogens used in hormonal contraceptives are considered in detail starting on p. 2240.3.

High doses of oestrogen used in treating malignant disease should be used cautiously in patients with cerebrovascular disorders, coronary artery disease, or venous thromboembolism. They may exacerbate hypercalcaemia of malignancy.

Oestrogens should be used with caution in children because premature closure of the epiphyses may occur resulting in inhibited linear growth and small stature.

Women using topical formulations of estradiol should take care to avoid skin-to-skin contact with others for an appropriate time after application, according to advice in the licensed product information. Premature puberty in girls and gynaecomastia in boys have occurred in young children who have been inadvertently exposed to estradiol, by contact with the treated area of skin of women using a transdermal spray.

Oestrogens have been reported to interfere with some diagnostic tests such as those for thyroid function and glucose tolerance.

Breast feeding. Estradiol has been detected in breast milk after the use of pessaries containing 50 or 100 mg of estradiol.[1] The American Academy of Pediatrics considers that estradiol is usually compatible with breast feeding.[2]

1. Nilsson S, *et al.* Transfer of estradiol to human milk. *Am J Obstet Gynecol* 1978; 132: 653–7.
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 27/06/08)

Cosmetic use. Use of cosmetic products containing oestrogens has led to adverse effects such as precocious puberty in children[1,2] and gynaecomastia or postmenopausal bleeding in adults.[1] Such products have been used by a greater proportion of African Americans than any other ethnic group in the USA, and it has been hypothesised that this may have contributed to the observations of earlier onset of puberty in girls[3,4] and increased risk of breast cancer in young women.[4]

1. Anonymous. Estrogens in cosmetics. *Med Lett Drugs Ther* 1985; 27: 54–5.
2. Tiwary CM. Premature sexual development in children following the use of estrogen- or placenta-containing hair products. *Clin Pediatr (Phila)* 1998; 37: 733–9.
3. Li S-T, *et al.* Hormone-containing hair product use in prepubertal children. *Arch Pediatr Adolesc Med* 2002; 156: 85–6.
4. Donovan M, *et al.* Personal care products that contain estrogens or xenoestrogens may increase breast cancer risk. *Med Hypotheses* 2007; 68: 756–66.

Pregnancy. Although gross abnormalities of the genitourinary tract have been reported in the male offspring of women who took diethylstilbestrol during pregnancy there is conflicting evidence as to whether the oestrogen produced an increased risk of abnormalities, infertility, or testicular cancer in such offspring (see p. 2268.3). The male fetus is normally protected from the feminising effects of the natural oestrogens in the uterine environment by the early development of the testes and the secretion of male hormones.[1] However, there has been considerable concern about a rising incidence of disorders of the male reproductive tract, and a reduction in sperm counts, which has been noted in the last 20 to 30 years. It has been hypothesised that overexposure of male fetuses to environmental oestrogens derived from pollutants such as pesticides and plastics may be responsible for this decline,[2,3] although some dispute this.[4] A systematic review[5] of epidemiological data found no strong evidence to link fetal exposure to oestrogens (as pharmaceuticals or pollutants) with reduced sperm count, cryptorchidism, or hypospadias, although there was some evidence to support a possible link with testicular cancer.

For discussion of the lack of effects of hormonal contraceptives on the fetus, including evidence that they are unlikely to increase the risk of hypospadia in the male fetus, see Pregnancy, under Precautions of Hormonal Contraceptives, p. 2242.1.

1. Mittwoch U, *et al.* Male sexual development in "a sea of oestrogen". *Lancet* 1993; 342: 123–4.
2. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993; 341: 1392–5.
3. de Kretser DM. Declining sperm counts. *BMJ* 1996; 312: 457–8.
4. Thomas JA. Falling sperm counts. *Lancet* 1995; 346: 635.
5. Storgaard L, *et al.* Male reproductive disorders in humans and prenatal indicators of estrogen exposure: a review of published epidemiological studies. *Reprod Toxicol* 2006; 21: 4–15.

Veterinary use. An FAO/WHO expert committee examining the risks from residues of veterinary drugs in foodstuffs established an acceptable daily intake for estradiol, but concluded that there would be no need to specify a numerical maximum residue limit for estradiol in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that in the EU the use of steroidal hormones such as oestrogens in veterinary practice is restricted, and their use as growth promotors is banned.

There is concern about the effect of environmental oestrogens on male fertility and development, see Pregnancy, above.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 27/06/08)

Interactions

Interactions involving estradiol and other oestrogens used in menopausal HRT are covered on p. 2251.1. Interactions for oestrogens used in hormonal contraceptives are covered on p. 2242.3.

Pharmacokinetics

In general, estradiol and other oestrogens are readily absorbed from the gastrointestinal tract and through the skin or mucous membranes. However, the natural unconjugated oestrogens such as estradiol undergo extensive first-pass metabolism in the gastrointestinal tract and liver after oral doses. They are, therefore, generally not orally active, although a micronised preparation of estradiol has sufficient bioavailability (3 to 5%) to be orally active. Estradiol is metabolised in part to less active oestrogens such as estriol and estrone. Synthetic oestrogens produced by alkylation of the C17 position, such as ethinylestradiol, are more slowly metabolised and are therefore orally active. Conjugated oestrogens, which are essentially oestrogen metabolites, are also orally active because they are hydrolysed by enzymes in the lower gastrointestinal tract allowing absorption of the active oestrogen. Vaginal, transdermal, intranasal, or parenteral use of oestrogens also avoids first-pass hepatic metabolism. Plasma-estradiol concentrations are reported to reach a peak 1.5 to 2 hours after an oral dose, and again at about 8 hours due to enterohepatic recycling. Estradiol esters are rapidly hydrolysed to free estradiol when given orally. After intramuscular injection of the esters, absorption is prolonged.

Oestrogens are extensively bound to plasma proteins. Naturally occurring oestrogens such as estradiol are mainly bound to sex-hormone binding globulin. Conversely, ethinylestradiol is mostly bound to albumin.

Oestrogens are metabolised in the liver. A variety of sulfate and glucuronide conjugates are formed, and these are excreted in the urine and the bile. Those excreted in the bile undergo enterohepatic recycling or are excreted in the faeces.

References to the pharmacokinetics of estradiol[1-4] and other oestrogens.[5,6]

1. Kuhnz W, *et al.* Pharmacokinetics of estradiol, free and total estrone, in young women following single intravenous and oral administration of 17 β -estradiol. *Arzneimittelforschung* 1993; 43: 966–73.
2. Schubert W, *et al.* Pharmacokinetic evaluation of oral 17 β -oestradiol and two different fat soluble analogues in ovariectomized women. *Eur J Clin Pharmacol* 1993; 44: 563–8.
3. Baker VL. Alternatives to oral estrogen replacement: transdermal patches, percutaneous gels, vaginal creams and rings, implants, other methods of delivery. *Obstet Gynecol Clin North Am* 1994; 21: 271–9.
4. Price TM, *et al.* Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 β -estradiol. *Obstet Gynecol* 1997; 89: 340–5.
5. Stumpf PG. Pharmacokinetics of estrogen. *Obstet Gynecol* 1990; 75 (suppl): 9S–14S.
6. O'Connell MB. Pharmacokinetic and pharmacologic variation between different estrogen products. *J Clin Pharmacol* 1995; 35 (suppl): 18S–24S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aerodiol; Estraderm†; Estradot†; Estreform; Etrosteron; Eutocol; Evorel; Ginatex; Ginediol; Hormodiol; Lindisc; Oestro Gel; Progynon; Progynova; Ronfase; Rontagel; Trial Gel; Trial SAT; *Austral.*: Aerodiol†; Climara; Estraderm; Estradot; Estrofem; Femtran; Menorest†; Primogyn Depot†; Progynova; Sandrena; Vagifem; Zumenon; *Austria*: Climara; Dermestril; Estradot; Estramon; Estrofem; Estrogel; FemSeven; Klimapur; Linoladiol; Menorest†; Progynon†; Progynova; Systen; Vagifem; *Belg.*: Aerodiol†; Climara; Dermestril; Estraderm; Estreva; Estrofem; Feminova; Meno-Implant; Oestrogel; Progynova; Systen; Vagifem; Vivelle; Zumenon; *Braz.*: Aerodiol; Avicis; Benzo-Ginoestril; Climaderm; Estradelle†; Estradot; Estreva; Estrofem; Fem 7; Hormodose; Lindisc; Merimono; Natifa; Oestrogel; Primogyna; Riselle; Sandrena; Systen; Tegan; *Canad.*: Climara; Divigel; Estrace; Estraderm; Estradot; Estring; Estrogel; Oesclim; Vagifem; *Chile*: Climaderm†; Dermatrans†; Enadiol†; Episetrol†; Estranova E†; Estreva; Farlutes†; Fem 7; Femalon; Femiderm; Femidot†; Ginoderm; Hormogel; Mirion; Primaquin; Progynova; Sandrena; Transvital; Vagifem; *China*: Climara (康美华); Dermestril (得美柔)†; Estrofem (诺坤复); Fem 7 (松奇); Happier (更乐); Oestrogel (爱斯妥); Progynova (补佳乐); Xie Kun (协坤); Yi Er (伊尔); Yi Tai Li (宜泰丽); *Cz.*: Agofollin; Climara; Dermestril; Divigel; Estraderm†; Estradot†; Estrahexal; Estrapatch; Estrimax; Estrofem; Linoladiol N; Neofollin; Octodiol†; Oestrogel; Riselle; Systen; Vagifem; *Denm.*: Climara†; Divigel; Estreva†; Estring; Estrofem; Estrogel; Evorel; Femanest; Progynon; Systen Conti; Vagifem; Vivelle Dot; *Fin.*: Climara; Dermestril†; Divigel; Estradot; Estrena; Estring; Estrofem; Estrogel; Evorel; FemSeven; Merimono†; Progynova; Vagifem; Zumenon; *Fr.*: Climara; Delidose; Dermestril; Estraderm†; Estrapatch; Estrofem; Oesclim; Oestrodose; Oestrogel; Oromone; Progynova; Provames; Thais; Vivelledot; *Ger.*: Cutanum†; Dermestril; Estrabeta†; Estraderm†; Estradot; Estramon†; Estreva; Estrifam; Estring; Estronorm†; Fem 7; Femoston mono; Gynokadin; Gynopolar; Linoladiol N; Merimono; Progynova; Sisare mono†; Tradelia; Vagifem; *Gr.*: Aerodiol; Climara; Dermestril; Estraderm TTS; Estradot; Estramon; Estring; Estrofem; Estrogel†; Menorest; Oesclim; Oestrogel; Progynon; Systen; Vagifem; *Hong Kong*: Dermestril†; Estraderm†; Estreva; Estrofem; Oestrogel; Progynova†; Vagifem; *Hung.*: Calidiol†; Dermestril; Divigel; Estraderm†; Estramon†; Estrapatch†; Estrimax; Estrofem; FemSeven†; Linoladiol N; Oestrogel†; Vagifem; *India*: Divigel; E2; Estraderm; Estrofem; ETS; Evalon; Oestrogel; *Indon.*: Estreva†; Fem 7†; Progynova; *Irl.*: Aerodiol†; Climara; Dermestril; Divigel; Episetrol†; Estraderm†; Estradot; Estreva†; Estrofem; Evorel; Fematab; Oestrogel; Vagifem; *Israel*: Estraderm†; Estrofem; Evorel; Oestrodose†; Oestrogel; Progynova; Vagifem; *Ital.*: Armonil; Climara; Dermestril; Epheliа†; Episetrol; Esclimat†; Estraderm; Estrodose; Estrofem; FemSeven; Gelestra; Ginaikos; Progynova; Sandrena; Systen; Vagifem; Zerella; *Malaysia*: Divigel; Oestrogel; Progynova; *Mex.*: Armistor†; Benzo-Ginestryl; Climaderm; Essventia; Estraderm†; Estramon; Estreva; Evorel; Fem 7; Ginedisc; Oestrogel; Primogyn; Sandrena; Systen; *Mon.*: Estreva; Femsept; *Neth.*: Aerodiol; Cetura; Climara†; Dermestril†; Estraderm†; Estradot; Estreva†; Estrofem; Fem 7†; Meno-Implant; Ovestal†; Progynova; Systen; Vagifem; Zumenon; *Norw.*: Climara†; Estradot; Estring; Evorel; Progynova; Vagifem; *NZ*: Aerodiol†; Climara; Estraderm; Estradot; Estrofem; Femtran; Progynova; Vagifem; *Philipp.*: Climara; Estrofem; Progynova; Vagifem; *Pol.*: Calidiol; Climara; Divigel; Estraderm; Estradot; Estrapatch†; Estreva; Estrofem; Estroplast†; Fem 7; Oesclim; Progynova; Systen; Vagifem; *Port.*: Climara; Dermestril; Episetrol; Estraderm; Estradot; Estrapatch; Estreva; Estrofem; Femring†; Femsete; Oestrodose†; Vagifem; Zumenon; *Rus.*: Climara (Климара); Divigel (Дивигель); Estrimax (Эстримакс); Estrofem (Эстрофем); Oestrogel (Эстрожель); Progynova (Прогинова); *S.Afr.*: Climara; Estraderm; Estradot; Estring; Estro-Pause; Estrofem; Evorel; Femigel; Primogyn Depot†; Progynova; Vagifem; *Singapore*: Divigel; Estraderm; Estring; Estrofem; Menostar; Oestrogel; Progynova; Vagifem; *Spain*: Absorlent†; Alcis; Dermestril†; Endomina†; Esprasone†; Estraderm; Estradot; Estrapatch†; Estroffik†; Evopad; Meriestra; Oestraclin; Progynova; Vagifem; *Swed.*: Climara†; Divigel; Estradot; Evorel; Femanest; Oesclim†; Oestring; Progynon; Vagifem; *Switz.*: Climara; Divigel; Estradot; Estramon†; Estreva†; Estring; Estrofem N; Femoston mono; Oestrogel; Progynova; Sandrena†; Systen; Vagifem; Zumenon†; *Thai.*: Climara; Divigel; Ediol; Estrofem; Oestrogel; Postmenop; Progynon†; Progynova; Vagifem†; *Turk.*: Aerodiol; Akrofolline; Climara; Estraderm; Estramon; Estrava; Estrofem; Fem 7; Femijel; Vagifem; *UK*: Bedol; Climaval; Elleste-Solo; Estraderm; Estradot; Estring; Evorel; Fematrix†; FemSeven; Oestrogel; Progynova; Sandrena; Vagifem; Zumenon; *Ukr.*: Divigel (Дивигель); Estramon (Эстрамон); Oestrogel (Эстрожель); Progynova (Прогинова); *USA*: Alora; Climara; Delestrogen; depGynogen; Depogen; Divigel; Elestrin; Esclim†; Estrace; Estraderm; Estrasorb; Estring; Estrogel; Evamist; FemPatch; Femring; Femtrace; Gynodiol; Menostar; Minivelle; Vagifem; Valergen; Vivelle; *Venez.*: Aerodiol; Climaderm; Estradot; Estrogel; FemSeven; Progynova.

Multi-ingredient Preparations. *Arg.*: Activelle; Angeliq; Atrimon; Ciclocur; Climene; Cristerona; Cyclofem; Disequens; Dos Dias N; Eos; Equifem; Estalis Sequi†; Estalis†; Estracomb†; Estragest; Evorel Conti; Evorel Sequi; Farludiol Ciclo; Farludiol; Fempack; Gadofem; Gynodian Depot; Hosterona; Kliogest; Lubriderm; Menstrogen†; Mesigyna; Patector; Perlutal; Prefest; Primosiston; Rubi; Supligol NF; Totelle Ciclico; Totelle Continuo; Trial Combi; Trial Gest; Trisequens; *Austral.*: Angeliq; Climen†; Estalis Continuous; Estalis Sequi; Estracomb; Femoston; Kliogest; Kliovance; Qlaira; Trisequens; Zoely; *Austria*: Activelle; Angeliq; Climen; Duokliman; Estalis Sequens†; Estalis; Estracomb†; Femoston Conti; Femoston; FemSeven Combi; Gynodian Depot; Kliogest; Mericomb; Merigest; Perikliman; Qlaira; Sequidot 2-Phasen; Trisequens; *Belg.*: Activelle; Angeliq; Climen; Climodien; Cyclocur; Diviplus; Diviva; Duogestan; Estalis; Estracombi; Feminova Plus; Femoston Conti; Femoston; Kliogest; Naemis; Novofem; Qlaira; Trisequens; *Braz.*: Activelle; Angeliq; Avaden; Ciclоprimogyna; Cliane; Climene; Cyclofemina; Daiva; Dilena; Elamax; Estalis SQ; Estalis; Estandron P; Estragest; Femoston Conti; Femoston; Gestadinona; Gineane; Kliogest; Lindisc Duo; Mericomb; Merigest; Mesigyna; Natifa Pro; Noregyna; Perlutan; Prefest; Preg-Less; Pregnolan; Suprelle; Suprema; Systen Conti; Systen Sequi; Totelle Ciclo; Totelle; Trinestril; Trisequens; Uno Ciclo; *Canad.*: Activelle; Angeliq; Climara Pro; Estalis; Estracomb†; *Chile*: Activelle; Altesse; Angeliq; Avaden†; Cliane; Climene; Clinomat; Enadiol CC†; Enadiol MP†; Enadiol Neta†; Estandron Prolongado†; Estracomb†; Estragest; Estranova 30 Simple†; Estranova CC†; Farlupost†; Fem 7 Combi; Femoston Conti; Femoston; Ginefolin; Ginotex; Gynodian Depot; Kilios; Kliogest; Lovelle Ciclico; Lovelle Continuo; Mesigyna; Novafem; Primaquin MP Continuo†; Primaquin MP†; Progyluton; Totelle Ciclico; Totelle Continuo; Trisequens; Unalmes; *China*: Activelle (诺更宁); Angeliq (安今益); Climen (克龄灵); Femoston (芬鸣通); Lunella (月纳); Novofem; Trisequens (诺康律); Yi Wei Xian (逸维仙); *Cz.*: Activelle; Alpicort F; Angeliq; Climen; Divina; Diviseq; Estalis Sequi†; Estalis†; Femoston Conti; Femoston Mini; Femoston; Folivirin; Gynodian Depot; Gynovel; Indivina; Kliane; Klimodien; Klimonorm; Kliogest; Noviana; Novofem; Pausogest†; Qlaira; Sequidot†; Systen Conti; Systen Sequi; Trisequens; *Denm.*: Activelle; Angemin; Climodien†; Cliovelle; Divina Plus; Divina; Estracomb†; Evo-Conti; Evo-Sequi; Femanor; Femasekvens; Indivina; Kliogest; Novofem; Nuvelle†; Qlaira; Trevina; Trisekvens; Trisequens; Zoely; *Fin.*: Activelle; Angeliq; Cliovelle; Cyclabil†; Divina; Divitren; Estalis Sekvens†; Estalis; Evorel Conti; Evorel Sequi; Femilar; Femoston Conti; Femoston; FemSeven Combi†; Indivina; Kliogest; Mericomb†; Merigest†; Novofem; Qlaira; Sequidot; Trisekvens; *Fr.*: Activelle; Angeliq; Avadene; Climaston; Climaston; Climene; Climodiene; Divina; Duova; Kliogest; Novofemme; Qlaira; Trisequens; *Ger.*: Activelle; Alpicort F; Angeliq; Climen; Climodien; Clionara; Cliovelle; Crinohormal fem; Cyclo-Progynova N; CycloOstrogynal; Estalis Sequi†; Estragest; Fem 7 Combi; Fem 7 Conti; Femoston Conti; Femoston; Gianda†; Gynamon†; Gynodian Depot; Indivina; Klimonorm; Kliogest N; Lafamme; Linoladiol-H N; Mericomb; Merigest; Novofem; Osmil†; Ostronara; Qlaira; Sequidot; Sisare 28†; Sisare†; Trisequens; Wellnara; *Gr.*: Activelle; Angeliq; Climodien; Cyclacur; Divina; Estalis Sequi; Estalis Sequidot; Estalis; Estopause; Estracomb TTS; Femaston; Kliogest; Nuvelle; Qlaira; Systen Conti; Systen Sequi; Trisequens; *Hong Kong*: Activelle; Angeliq; Climen 28†; Cyclofem; Dilena†; Estracomb†; Femoston Conti†; Femoston; Hormonin†; Kliogest; Novofem; Trisequens; *Hung.*: Activelle; Alpicort F; Angeliq; Climen†; Divina; Estracomb†; Estragest; Femoston; FemSeven Combi†; Indivina; Klimonorm; Kliogest; Novofem; Pausogest; Qlaira; Triaklim; Trisequens; Tulita; *India*: Kemicetine Antiozena; Mixogen; *Indon.*: Angeliq; Climen 28; Cyclo-Progynova; Cyclofem†; Femoston; Mediol†; Renodiol; *Irl.*: Activelle; Allurene†; Angeliq; Estalis Sequi†; Estalis†; Estracombi†; Evorel Conti; Femoston Conti; Femoston; FemSeven Conti; FemSeven Sequi†; Femurest-Conti; Indivina; IOA; Kliogest; Naemis†; Novofem; Qlaira; Trisequens; Zoely; *Israel*: Activelle; Angeliq; Eviana; Evorel Conti; Evorel Sequi; Kliogest; Novofem; Progyluton; Qlair; Trisequens; *Ital.*: Activelle; Angeliq; Climen; Combiseven; Estalis Sequi; Estracomb†; Femity; Femoston Conti; Femoston; Filena; Gynodian Depot; Klaira; Kliogest; Menovis; Naemis; Pausene; Trisequens; *Malaysia*: Activelle; Angeliq; Climen; Duogynon; Femoston Conti; Femoston; Progyluton; *Mex.*: Anafertin; Angeliq; Avaden; Binodian; Cliane; Climene; Cyclofemina; Damax; Despamen; Dilena; Estalist; Estracomb; Evorel Conti; Genofort; Gravidinona; Lutalmin; Lutoginestryl F; Mesigyna; Metrigen Fuerte; Nostidyn; Patector; Perludil; Perlutal; Prefest; Primoson-F; Proger-F; Progyluton; Totelle Continuo; Totelle Secuencial; Xofemina; Yectames; *Mon.*: FemseptCombi; Femseptevo; Naemis; Zoely; *Neth.*: Activelle; Allurene†; Angeliq; Climaston Continu; Climenet†; Climodien; Cyclocur†; Estalis Sequi†; Estalist†; Estandron Prolongatum†; Estracomb†; Eviana; Fem 7 Sequi†; Femoston Continu; Femoston; Femphascyl Continu; Femphascyl; Ioa; Kliogest; Lafamme; Naemist†; Novofem; Qlaira; Trisequens; Zoely; *Norw.*: Activelle; Climodien†; Cliovelle; Estalis Sekvens†; Estalis; Eviana; Indivina; Kliogest†; Novofem; Qlaira; Sequidot; Trisekvens; Zoely; *NZ*: Cllanet†; Femoston; Kliogest; Kliovance; Nuvelle; Trisequens; *Philipp.*: Angeliq; Climen 28; Femoston†; Kliogest; *Pol.*: Activelle; Alpicort E; Angeliq; Climen; Cliovelle; Cyclo-Progynova; Divina; Diviseq; Estalis Sequi†; Estalis; Estracomb; Fem 7 Combi; Femoston Conti; Femoston Mini; Femoston; Gynodian Depot†; Indivina; Klimonorm; Kliogest; Novofem; Qlaira; Systen Conti; Systen Sequi; Trisequens; *Port.*: Activelle; Allurene; Angeliq; Avadene; Climen; Climodien; Dilena; Estalis Sequi; Estalis; Estracomb†; Femoston 1/5; Femoston; Femsete Combi; Femsete Evo; Kliogest; Lafamme; Naemis; Novofem; Nuvelle; Progyluton; Qlaira; Trisequens; *Rus.*: Angeliq (Анжелик); Climen (Климен); Climodien (Климодиен); Cyclo-Progynova (Цикло-прогинова); Divina (Дивина); Diviseq (Дивисек); Divitren (Дивитрен)†; Femoston (Фемостон); Femoston 1/5 (Фемостон 1/5); Gynodian Depot (Гинодиан Депо)†; Indivina (Индивина); Klimonorm (Климонорм); Kliogest (Клиогест); Pausogest (Паузогест); Triaklim (Триаклим); Trisequens (Трисеквенс); *S.Afr.*: Activelle; Angeliq; Climen; Divinat; Estalis; Estracombi†; Estro-Pause N; Evorel Conti; Evorel Sequi; Femoston Conti; Femoston; Kliogest; Mixogen†; Novofem; Postoval; Prefesta†; Primodian Depot†; Trisequens; Trivina†; *Singapore*: Activelle; Climen; Estracomb; Femoston Conti; Femoston; Kliogest†; Progyluton; Qlaira; Trisequens; Unijab; *Spain*: Absorlent Plus†; Activelle; Angeliq; Climen; Climodien; Duofemme; Endomina Plus†; Estalis Sequi; Estalis; Estracomb†; Eviana; Merigest Sequi†; Merigest†; Mevaren; Nuvelle†; Perifem; Progyluton; Qlaira; Trisequens; Zoely; *Swed.*: Activelle; Angemin; Climodien†; Cliovelle; Divina Plus; Estalis; Eviana; Femanor; Femasekvens; Indivina; Kliogest†; Novofem; Qlaira; Sequidot; Trisekvens†; Trivina; Zoely; *Switz.*: Activelle; Alpicort F; Angeliq; Climen; Cyclacur; Diviseq†; Estalis Sequi†; Estalis; Estracomb†; Estragest; Estranor; Femoston Conti; Femoston; Gynodian Depot; Indivina; Kliogest N; Mericomb†; Merigest†; Novofem; Sequidot; Systen Conti; Systen Sequi; Triaval†; Trisequens; Zoely; *Thai.*: Activelle; Angeliq; Climen; Cyclo-Progynova; Diviseq†; Duoton; Femoston 1/10; Femoston Conti; Havina†; Indivina†; Klimonorm†; Phenokinon-F; Primodian Depot†; *Turk.*: Activelle; Angeliq; Climen; Climodien; Cyclo-Progynova; Di-Pro; Divina; Estandron Prolan; Estracombi; Femoston; Kliogest; Mesigyna; Trisequens; *UK*: Angeliq; Climagest; Climesse; Clinorette; Cyclo-Progynova 1 mg; Cyclo-Progynova 2 mg; Elleste Duet Conti; Elleste-Duet; Estracombi†; Evorel Conti; Evorel Sequi; Femapak†; Femoston Conti; Femoston; FemSeven Conti; FemSeven Sequi; Hormonin; Indivina; Kliofem; Kliovance; Novofem; Nuvelle Continuous; Nuvelle†; Qlaira; Tridestra; Trisequens; Zoely; *Ukr.*: Angeliq (Анжелик); Climen (Климен); Divina (Дивина)†; Femoston (Фемостон); Indivina (Индивина)†; Klimodien (Климодиен)†; Klimonorm (Климонорм); Pausogest (Паузогест)†; Revmelid (Ревмелид)†; *USA*: Activella; Angeliq; ClimaraPro; CombiPatch; Depo-Testadiol†; Depotestogen†; Mimvey; Natazia; Prefest; *Venez.*: Avaden; Cliane; Climene; Estragest; Femoston Conti; Femoston; Ginecosid; Ginecosid; Gynodian Depot; Mesigyna; Progyluton; Totelle Ciclico; Totelle Continuo.

Pharmacopoeial Preparations

BP 2014: Estradiol and Norethisterone Acetate Tablets; Estradiol and Norethisterone Tablets; Estradiol Injection; Estradiol Transdermal Patches;

USP 36: Estradiol and Norethindrone Acetate Tablets; Estradiol Cypionate Injection; Estradiol Tablets; Estradiol Transdermal System; Estradiol Vaginal Cream; Estradiol Vaginal Inserts; Estradiol Valerate Injection.

Estrapronicate *(rINN)*

Estrapronicato; Estrapronicatum; Эстрапроникат.

Oestradiol 17-nicotinate 3-propionate.

$C_{27}H_{31}NO_4$=433.5

CAS — 4140-20-9.

UNII — BC621AC03L

Profile

Estrapronicate is a derivative of estradiol (p. 2271.1) with nicotinic acid. It has been used as an ingredient of a combined preparation with an anabolic steroid and a progestogen for osteoporosis.

Estriol *(BAN, rINNM)*

Estrioli; Estriolis; Estriolum; Follicular Hormone Hydrate; Oestriol; Östriol; Ösztriol; Theelol; Эстриол.

Estra-1,3,5(10)-triene-3,16α,17β-triol.

$C_{18}H_{24}O_3$=288.4

CAS — 50-27-1.

ATC — G03CA04.

ATC Vet — QG03CA04; QG03CC06.

UNII — FB33469R8E.

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

Ph. Eur. 8: (Estriol). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol.

USP 36: (Estriol). A white or practically white, odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol; soluble in acetone, in chloroform, in dioxan, in ether, and in vegetable oils. Store in airtight containers.

Estriol Sodium Succinate *(BAN, rINNM)*

Estriol, Succinate Sodique d'; Estriol, succinato sódico de; Estrioli Natrii Succinas; Oestriol Sodium Succinate; Succinato sódico de estriol; Эстриола Натрия Сукцинат.

Disodium 3-hydroxyestra-1,3,5(10)-triene-16α,17β-diyl disuccinate.

$C_{26}H_{30}Na_2O_9$=532.5.

CAS — 113-22-4.

ATC — G03CA04.

ATC Vet — QG03CA04.

UNII — 64I100CU65.

Estriol Succinate *(BAN, rINN)*

Estriol, Succinate d'; Estriol, succinato de; Estrioli Succinas; Estriolisuksinaatti; Estriolsuccinat; Oestriol Succinate; Succinato de estriol; Эстриола Сукцинат.

3-Hydroxyestra-1,3,5(10)-triene-16α,17β-diyl di(hydrogen succinate).

$C_{26}H_{32}O_9$=488.5.

CAS — 514-68-1.

ATC — G03CA04.

ATC Vet — QG03CA04.

UNII — AS13K2DY03.

Profile

Estriol is a naturally occurring oestrogen with actions and uses similar to those described for estradiol (p. 2271.1).

It is used for menopausal HRT (p. 2244.1). When oestrogens are given to women with a uterus, a progestogen is required, particularly if used long term. Oral doses of estriol 4 to 8 mg daily may be used initially, followed by a gradual reduction to the lowest effective dose. Estriol has also been given with other natural oestrogens such as estradiol and estrone (see below); usual doses of estriol have ranged from about 0.25 to 2 mg daily. Estriol may be used intravaginally for the short-term treatment of menopausal atrophic vaginitis and kraurosis vulvae. A dose of 500 micrograms may be given as a 0.01% or 0.1% cream or as a pessary; initial treatment may be given once daily, then reduced to twice each week.

Estriol has also been given orally for infertility (p. 2253.1) caused by poor cervical penetration, in a dose of 1 to 2 mg daily on days 6 to 15 of the menstrual cycle. The dose may be increased if necessary each month, until an optimal effect on the cervical mucous is obtained. Doses of up to 8 mg daily on treatment days may be needed.

Estriol succinate has also been given orally in the treatment of menopausal disorders. The sodium succinate salt has been used parenterally in the treatment of haemorrhage and thrombocytopenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Colpoestriol; Menodim; Orgestriol; ***Austral.***: Ovestin; ***Austria***: Ortho-Gynest; Ovestin; ***Belg.***: Aacifemine; Ortho-Gynest; ***Braz.***: Estriopax; Hormocervix; Hormoniol; Ovestrion; Styptanon†; ***Chile***: Ovestin; Sinapause; Vacidox; ***China***: Ovestin (欧维婷); Yi Te Le (伊特乐); ***Cz.***: Ortho-Gynest; Ovestin; ***Denm.***: Ovestin; ***Fin.***: Ovestin; Pausanol; ***Fr.***: Gydrelle; Physiogine; Trophicreme; ***Ger.***: Cordes Estriol; OeKolp; Oestro-Gynaedron M; Ortho-Gynest; Ovestin; Synapause E†; Xapro; ***Gr.***: Ovestin; ***Hung.***: Estrokad; Ortho-Gynest; Ovestin; ***Indon.***: Ovestin; ***Irl.***: Ortho-Gynest†; Ovestin; ***Israel***: Ortho-Gynest; Ovestin; ***Ital.***: Colpogyn; Ortho Gynest Depot; Ovestin†; Trofogin; ***Jpn***: Estriel; ***Mex.***: Ortho-Gynest; Ovestin; Sinapause; ***Neth.***: Synapause-E_3; ***Norw.***: Ovesterin; ***NZ***: Ovestin; ***Philipp.***: Ovestin; ***Pol.***: Oekolp; Ortho-Gynest; Ovestin; ***Port.***: Ovestin; Pausigin; ***Rus.***: Estrokad (Эстрокад); Ovestin (Овестин); ***S.Afr.***: Synapause; ***Spain***: Ovestinon; ***Swed.***: Ovesterin; ***Switz.***: Oestro-Gynaedron; Ortho-Gynest; Ovestin; ***Thai.***: Ovestin; ***Turk.***: Ovestin; ***UK***: Gynest; Ortho-Gynest†; Ovestin; ***Ukr.***: Ovestin (Овестин); ***Venez.***: Ortho-Gynest; Ovestin.

Multi-ingredient Preparations. ***Arg.***: Tropivag Plus; ***Austria***: Gynoflor; ***Belg.***: Gynoflor; ***Cz.***: Gynoflor; ***Fr.***: Florgynal; Trophigil; ***Ger.***: CycloOstrogynal; Gynoflor; ***Hong Kong***: Gynoflor; Hormonin†; ***Hung.***: Gynoflor; ***Ital.***: Donaflor; ***Malaysia***: Gynoflor; ***Pol.***: Gynoflor; ***Port.***: Gynoflor; ***Rus.***: Gynoflor E (Гинофлор Э); ***Switz.***: Gynoflor; ***Thai.***: Gynoflor; ***Turk.***: Gynoflor; ***UK***: Hormonin; ***Ukr.***: Gynoflor (Гинофлор).

Pharmacopoeial Preparations
BP 2014: Estriol Cream.

Estrone *(BAN, rINN)*

Estron; Estrona; Estroni; Estronum; Folliculina; Follicular Hormone; Folliculin; Ketohydroxyoestrin; Oestrone; Östron; Эстрон.

3-Hydroxyestra-1,3,5(10)-trien-17-one.

$C_{18}H_{22}O_2$=270.4.

CAS — 53-16-7.

ATC — G03CA07.

ATC Vet — QG03CA07; QG03CC04.

UNII — 2DI9HA706A.

Pharmacopoeias. In *US*.

USP 36: (Estrone). Odourless, small white crystals or white to creamy-white crystalline powder. Practically insoluble in water; soluble 1 in 250 of alcohol and 1 in 110 of chloroform at 15 degrees; soluble 1 in 50 of boiling alcohol, 1 in 33 of boiling acetone, 1 in 145 of boiling benzene, and 1 in 80 of boiling chloroform; soluble 1 in 50 of acetone at 50 degrees; soluble in dioxan and in vegetable oils; slightly soluble in solutions of fixed alkali hydroxides. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Estrone is a naturally occurring oestrogen with actions and uses similar to those described for estradiol (see p. 2271.1).

For menopausal HRT (see p. 2244.1) estrone has been given orally at a dose of 1.4 to 2.8 mg daily in a cyclical or continuous regimen, as a combination product with estradiol and estriol (see p. 2274.3). Estrone has also been given by intramuscular injection in oily solutions and aqueous suspensions. When used specifically for menopausal atrophic vaginitis, estrone has been given vaginally. If used in women with a uterus, estrone by any route should be given with a progestogen.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Estragyn; ***USA***: Kestrone.

Multi-ingredient Preparations. ***Hong Kong***: Hormonin†; ***Mon.***: Synergon; ***Port.***: Gretalvite; ***Spain***: Cicatral; Grietalgen; ***Thai.***: Metharmon-F†; ***Turk.***: Synergon; ***UK***: Hormonin.

Pharmacopoeial Preparations
USP 36: Estrone Injectable Suspension.

Estropipate *(BAN)*

Estropipato; Piperazine Estrone Sulfate; Piperazine Oestrone Sulphate; Эстропинате.

Piperazine 17-oxoestra-1,3,5-(10)-trien-3-yl hydrogen sulphate.

$C_{18}H_{22}O_5S,C_4H_{10}N_2$=436.6.

CAS — 7280-37-7.

UNII — SVI38UY019.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Estropipate). A white or almost white crystalline powder. Very slightly soluble in water, in alcohol, in chloroform, and in ether.

USP 36: (Estropipate). A white to yellowish-white fine crystalline powder, odourless or may have a slight odour. Very slightly soluble in water, in alcohol, in chloroform, and in ether; soluble 1 in 500 of warm alcohol; soluble in warm water. Store in airtight containers.

Uses and Administration

Estropipate is a semisynthetic conjugate of estrone with piperazine that is used for menopausal HRT (see p. 2244.2). Its action is due to estrone (see above) to which it is hydrolysed in the body.

Estropipate is given orally for the short-term treatment of menopausal symptoms in doses ranging from 0.75 to 3 mg daily, given cyclically or continuously; doses up to 6 mg daily have also been given cyclically. Daily doses such as 0.75 mg cyclically or 1.5 mg continuously may be given for the prevention of postmenopausal osteoporosis, but oestrogen therapy is generally reserved for women who are at significant risk and who cannot be given non-hormonal treatment. In women with a uterus estropipate should be used with a progestogen. Estropipate has also been used short term for menopausal atrophic vaginitis as a vaginal cream containing 0.15%; 2 to 4 g of cream is applied daily. In the treatment of female hypogonadism, castration, and primary ovarian failure, estropipate is given orally in doses of 1.5 to 3 mg daily, in a cyclical regimen; higher doses of up to 9 mg daily given cyclically have also been used.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). See also under Hormone Replacement Therapy, p. 2246.3.

Interactions

See under Hormone Replacement Therapy, p. 2251.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Genoral; Ogen†; ***Canad.***: Ogen; ***Indon.***: Ogen†; ***S.Afr.***: Ortho-Est; ***UK***: Harmogen†; ***USA***: Ogen.

Pharmacopoeial Preparations
BP 2014: Estropipate Tablets;
USP 36: Estropipate Tablets; Estropipate Vaginal Cream.

Ethinylestradiol *(BAN, rINN)*

Aethinyloestradiolum; Ethinyl Estradiol; Ethinylestradiol; Ethinylestradiolum; Ethinyloestradiol; Etinilestradiol; Etinilestradiolis; Etinilöstradiol; Etinilösztradiol; Etinylestradiol; Etinyyliestradioli; Etynyloestradiol; NSC-10973; Этинилэстрадиол.

17α-Ethynylestra-1,3,5(10)-triene-3,17β-diol; 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol.

$C_{20}H_{24}O_2$=296.4.

CAS — 57-63-6.

ATC — G03CA01; L02AA03.

ATC Vet — QG03CA01; QL02AA03.

UNII — 423D2T571U.

NOTE. Compounded preparations of ethinylestradiol may be represented by the following names:

- Co-cyprindiol (*BAN*)—ethinylestradiol 35 parts and cyproterone acetate 2000 parts (w/w).

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

Ph. Eur. 8: (Ethinylestradiol). A white to slightly yellowish-white, crystalline powder. It shows polymorphism. Practically insoluble in water; freely soluble in alcohol; dissolves in dilute alkaline solutions. Protect from light.

USP 36: (Ethinyl Estradiol). A white to creamy white, odourless, crystalline powder. Insoluble in water; soluble in alcohol, in chloroform, in ether, in vegetable oils, and in solutions of fixed alkali hydroxides. Store in nonmetallic airtight containers. Protect from light.

Uses and Administration

Ethinylestradiol is a synthetic oestrogen with actions similar to those of estradiol (see p. 2271.2).

It is frequently used as the oestrogenic component of combined oral **contraceptive** preparations; a typical daily dose is 20 to 40 micrograms (for guidance on appropriate dose, see p. 2231.3). Ethinylestradiol betadex clathrate has been used similarly in combined oral contraceptives. Ethinylestradiol is also used in a combined contraceptive transdermal patch that releases 33.9 micrograms of ethinylestradiol daily with norelgestromin. A new patch is applied each week for 3 weeks of a 4-week cycle. Oestrogen exposure from such a patch may be higher than with a comparable oral contraceptive, and may be associated with a higher risk of venous thromboembolism (see p. 2238.1). A combined contraceptive vaginal ring device delivering an average of 15 micrograms ethinylestradiol daily with etonogestrel is also available; it remains in the vagina for 3 weeks and is then removed for a one-week break, after which a new ring is inserted. Ethinylestradiol has also been used orally as an emergency contraceptive (p. 2233.2) combined with levonorgestrel or norgestrel. A combined preparation of ethinylestradiol with the anti-androgen cyproterone is used for the hormonal treatment of acne (p. 1682.2) and hirsutism (p. 2262.1), particularly when contraception is also required (see Uses and Administration, under Cyproterone Acetate, p. 2261.2).

Ethinylestradiol has also been used for **menopausal HRT** (p. 2244.2), although natural oestrogens are usually preferred. Oral doses of 10 to 50 micrograms daily have been given cyclically (with a progestogen in women with a uterus), but preparations providing lower doses of 2.5 or 5 micrograms daily are also available.

For the treatment of female **hypogonadism**, doses of 10 to 50 micrograms daily on a cyclical basis have been used.

For the palliative treatment of **prostate cancer** (p. 712.3) doses of 150 micrograms to 1.5 mg have been given daily. Ethinylestradiol has also been used for palliation of malignant neoplasms of the **breast** (p. 702.1) in postmenopausal women.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* does include doses of ethinylestradiol. An initial oral dose of 2 micrograms daily

may be used in the management of **delayed puberty** (p. 2252.1) in girls. This may be increased every 6 months to 5 micrograms, then to 10 micrograms, then to 20 micrograms daily, according to response. After 12 to 18 months of treatment, a progestogen should be added for 7 days of each 28-day cycle. A daily dose of ethinylestradiol 20 micrograms with cyclical progestogen may then be used to maintain sexual maturation. For the prevention of constitutional **tall stature**, oral ethinylestradiol may be given to girls aged 2 to 12 years old in a dose of 20 to 50 micrograms daily (see also Growth Disorders in Estradiol, p. 2272.2).

Growth hormone provocation testing may be used in the diagnosis of growth hormone deficiency in children with growth retardation (p. 1918.3). However, the response can be blunted in prepubertal and peripubertal children, resulting in false negative results. Hormonal **pituitary priming** using ethinylestradiol has been tried in both boys and girls in order to increase responsiveness to the test,[1,2] although there appears to be no consensus on such use.[3] The *BNFC* includes an oral dose of 100 micrograms daily for 3 days before the test, for girls with a bone age above 10 years.

1. Loche S, *et al.* The growth hormone response to hexarelin in children: reproducibility and effect of sex steroids. *J Clin Endocrinol Metab* 1997; **82**: 861–4.
2. Coutant R, *et al.* Body composition, fasting leptin, and sex steroid administration determine GH sensitivity in peripubertal short children. *J Clin Endocrinol Metab* 2001; **86**: 5805–12.
3. Growth Hormone 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 22/08/08)

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Effects on calcium homoeostasis. Two patients with metastatic breast cancer given ethinylestradiol developed rapidly progressive irreversible and fatal hypercalcaemia, considered to be due to stimulation of osteolysis by the oestrogen.[1]

1. Cornbleet M, *et al.* Fatal irreversible hypercalcaemia in breast cancer. *BMJ* 1977; **1**: 145.

Effects on the liver. Cholestasis and pruritus developed in a liver transplant recipient receiving ethinylestradiol at a dose of 50 micrograms daily for the treatment of menorrhagia.[1] Symptoms subsided on withdrawal of ethinylestradiol but returned on its re-introduction.

1. Pedorkow DM, *et al.* Cholestasis induced by oestrogen after liver transplantation. *BMJ* 1989; **299**: 1080–1.

Interactions

See under Hormonal Contraceptives, p. 2242.3, and Hormone Replacement Therapy, p. 2251.1.

Reviews.

1. Zhang H, *et al.* Pharmacokinetic drug interactions involving 17 α-ethinylestradiol: a new look at an old drug. *Clin Pharmacokinet* 2007; **46**: 133–57.

Pharmacokinetics

Ethinylestradiol is rapidly and well absorbed from the gastrointestinal tract. The presence of an ethinyl group at the 17-position greatly reduces hepatic first-pass metabolism compared with estradiol, enabling the compound to be much more active by mouth, but there is some initial conjugation by the gut wall, and the systemic bioavailability is only about 40%. Ethinylestradiol is highly protein bound, but unlike naturally occurring oestrogens, which are mainly bound to sex-hormone binding globulin, it is principally bound to albumin. It is metabolised in the liver, initially by aromatic hydroxylation catalysed by the cytochrome P450 isoenzyme CYP3A4, to form 2-hydroxyethinylestradiol and various conjugated metabolites. These are excreted in urine and faeces. Metabolites undergo enterohepatic recycling.

References.

1. Back DJ, *et al.* The gut wall metabolism of ethinyloestradiol and its contribution to the pre-systemic metabolism of ethinyloestradiol in humans. *Br J Clin Pharmacol* 1982; **13**: 325–30.
2. Guengerich FP. Metabolism of 17 α-ethynylestradiol in humans. *Life Sci* 1990; **47**: 1981–8.
3. van den Heuvel MW, *et al.* Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception* 2005; **72**: 168–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Diva Total; *India*: Ethinorm-E; Lynoral; *Indon.*: Lynoral; *Neth.*: Lynoral; *Rus.*: Microfollin (Микрофоллин); *Switz.*: Elleacnelle; *Thai.*: NuvaRing; *USA*: Estinyl†.

Multi-ingredient Preparations. *Arg.*: Afrodita; Alell; Anubis; April; Avancel; Biofem 35†; Biofem; Cilest; Cuarcic†; Cuidafem; Damsel; Damsella; Diane; Dienopil; Diva; Divina; Dos Dias N; Elektra; Evelea; Evra; Femexin; Femiane; Florence; Ginelea T; Ginelea; Gynovin; Harmonet; Isis Fe; Isis; Jade; Kala; Kir; Kirum; Kirumelle; Livianne; Loette; Lutogynestryl; Marvelon; Maxima MD 24; Maxima; Mercilon; Mesconcept†; Microfem; Microgynon; Microvlar; Mileva; Minesse; Minulet; Miranova; Mirelle; Neogynon; Nordette; Norfen; Norgestrel Cex; Norgestrel Minor; Norgestrel Plus; Primosiston; Secret 28; Tess 35; Tridestan N; Tridette; Trinordiol; Triquilar; Umma; Venisse; Yasmin; Yasminelle; YAZ; Zinnia; *Austral.*: Brenda-35 ED; Brevinor; Diane; Estelle; Femoden ED†; Improvil; Juliet; Laila-35 ED; Levlen ED; Loette; Logynon ED; Marvelon; Microgynon; Microlevlen ED; Minulet; Monofeme; Nordette; Norimin; NuvaRing; Sequilar ED†; Synphasic; Trifeme; Trioden†; Triphasil; Triquilar; Valette; Yasmin; YAZ; *Austria*: Aliane; Balanca; Belara; Bellgyn; Cileste; Diane; Evra; Gracial; Gynovin; Harmonette; Lenea; Leonore; Liberel; Loette; Madinette; Madonella; Marvelon; Meliane; Mercilon; Microgynon; Midane; Minerva; Minesse; Minulet; Mirelle; Motion; NuvaRing; Ovranette; Ovysmen; Primosiston; Sequilar†; Sylgestrel; TriCilest; Trigynon†; Trinordiol; Trinovum; Triodena; Valette; Vivelle; Wave; Xylla; Xyliette; Yasmin; Yasminelle; YAZ; Yirala; Yris; *Belg.*: Cilest; Claudia; Cyprodiol†; Daphne; Desorelle†; Diane; Doccyproestra†; Docdonna†; Eleonor; Elisamylan; Evra; Femodene; Gestodelle; Gestofeme; Gracial; Gratiella; Harmonet; Lowette; Marvelon; Meliane; Mercilon; Microgynon; Minulet; Mirelle; Mylenamylan†; Nora-30; NuvaRing; Ovidol; Ovysmen; Ratiopharmeva†; Rimendia; Stediril 30; Tri-Minulet; Trigynon; Trinordiol; Trinovum; Triodene; Yasmin; Yasminelle; YAZ; *Braz.*: Adoless; Alexa; Allestra; Anfertil; Artemidis; Belara; Ciclo; Ciclofemme; Ciclogyn; Ciclovulon; Ciprane; Concepnor; Diane; Diclin; Diminut; Elani; Evanor; Evra; Femiane; Femina; Ferane 35; Fertnon; Gestinol; Gestradiol; Gestrelan; Ginesse; Gracial; Gynera; Harmonet; Level; Levordiol; Lizzy; Lovelle; Malu; Mercilon Conti; Mercilon; Microdiol; Micropil; Microvlar; Minesse; Minian; Minima; Minulet; Miranova; Mirelle; Neovlar; Nodclin; Nordette; Normamor; Novial; NuvaRing; Ovoresta†; Previane; Primera; Primeravinte†; Primosiston; Repopil; Selene; Siblima; Tamisa; Tantin; Tess; Trinordiol; Triquilar; Yasmin; YAZ; *Canad.*: Alesse; Apri; Aviane; Brevicon; Cyclen; CyEstra; Demulen; Diane; Evra; FemHRT; Linessa; Loestrin 1.5/30; Marvelon; Min-Ovral; Minestrin; NuvaRing; Ortho 0.5/35; Ortho 1/35; Ortho 7/7/7; Ortho-Cept; Ovral; Portia; Seasonale; Seasonique; Select 1/35; Synphasic; Tri-Cyclen; Triquilar; Yasmin; YAZ; *Chile*: Alesse†; Anovulatorio Micro-Dosis; Anuar; Anulette; Belara; Careza; Ciclidon; Ciclomex; Conti-Marvelon; Dahlia; Dal; Desoren; Diane; Dixi-35; Drina; Evilin; Evra; Femelle; Feminol; Femiplus; Femitres; Gianda; Gracial; Gynera; Gynorelle; Gynostat; Harmonet; Innova Cd; Lady-Ten 35; Lovinda; Mactex; Marvelon; Miafem; Microgen; Microgynon; Midalet; Minesse; Miniestrel; Minigest; Minulet; Miranova; Mirelle; Modutrol†; Neofam†; Neolette; Nordette; Nordiol; Norvetal; NuvaRing; Orlon; Primosiston; Tinelle; Tri-Ciclomex†; Tri-Mactex†; Trinordiol; Triquilar; Trolit; Vexa; Yasmin; YAZ; *China*: Compound Norethisterone (复方炔诺酮); Diane (达英); Duotrina (多日纳); Mercilon (美欣乐); Minulet (敏定偶); Triquilar (特居乐); Yasmin (优思明); Yiketing (谊可婷); *Cz.*: Adele; Artizia; Belanette; Belara; Bellune; Belusha; Chloe; Cilest; Circlet; Clormetin; Daylette; Diane; Dienille; Dienorette; Drosetil; Egretta; Eloine; Esete; Evra; Femoden; Gracial; Gravistat; Harmonet; Jangee; Jeanine; Katya; Kirga; Larabel†; Laurina; Lindynette; Loette; Logest; Lunafem; Madinelle; Maitalon; Marvelon; Mercilon; Microgynon; Milligest; Minerva; Minesse; Minisiston; Minulet; Mirelle; Natalya; Nelya; Novynette; NuvaRing; Pramino; Regulon; Softinelle; Stodette; Sunya; Sylviane; Tri-Minulet; Tri-Regol; Tricia; Trinordiol†; Trinovum; Triquilar; Vreya; Yadine; Yasminelle; YAZ; *Denm.*: Cilest; Daisynelle; Desorelle; Diane; Dianova; Dretine; Eloine; Estinette; Evra; Femelle; Femicept; Femigen; Feminil; Femistad; Finminette; Gestinyl; Gestodilat; Gestonette; Gracial; Harmonet; Lindynette; Loette; Malonetta; Marvelon; Mercilon; Microgyn; Milligest; Milna; Milvane; Minero; Minulet; Modina; Movinella; Neogynon†; Novynette; NuvaRing; Palandra; Rigevidon; Rubira; Tercette; Triafem; Triminetta; Trinordiol†; Trinovum†; Triquilar; Triregol; Vellena; Vreya; Yasmin; Yasminelle; YAZ; Zafira†; Zyrona; *Fin.*: Cilest; Cypretyl; Diane; Evra; Feminil; Femoden; Gestinyl; Gestodilat; Gracial; Harmonet; Laurette; Laurina; Linatera; Liofora; Marvelon; Meliane; Mercilon; Microgynon; Minero; Minulet; Miranova; Mirelle; Modina; NuvaRing; Palandra; Stefaminelle; Tasminetta; Tri-Femoden; Trikvilar; Vreya; Yasmin; Yasminelle; YAZ; *Fr.*: Adepal; Amarance; Belanette; Belara; Carlin; Cilest; Convuline; Cycleane†; Daily; Desobel; Diane; Drospibel; Edenelle; Efezial; Effiprev; Evanecia; Evepar; Evra; Harmonet; Holgyeme; Jasmine; Jasminelle; Jasminellecontinu; Lovavulo; Ludeal; Lumalia; Meliane; Melodia; Mercilon; Minerva; Minesse; Minidril; Miniphaset; Minulet; Moneva; NuvaRing; Optinesse; Ortho-Novum 1/35†; Pacilia; Perleane; Phaeva; Rimendia; Stediril; Sylviane; Tri-Minulet; Triafemi; TriCilest; Triella; Trinordiol; Varnoline; YAZ; *Ger.*: Aida; Asumate; Attempta; Balanca†; Belara; Bella†; Bellissima; Biviol; Chariva; Cilest; Clevia†; Conceplan M; Cyclosa†; Cyproderm; Cypronette†; Desmin; Diane; Enriqa; Ergaleat; Evaluna; Eve; Evra; Femigoa; Femigyne; Femovan; Femranette mikro†; Gravistat; illina†; Lamuna†; Leios; Leona; Liana; Lovelle; Madinette; Marvelon; Maxim; Microgynon; Minette; Minisiston; Minulet; Miranova; MonoStep; Morea; Neo-Eunomin; NovaStep; Novial; NuvaRing; Oviala; Oviol†; Ovoresta M†; Petibelle; Pink Luna; Pramino; Synphasec; Triette†; Trigoa; Trinovum; Triquilar; Trisiston; Valette; Verana; Yasmin; Yasminelle; YAZ; *Gr.*: Evra; Gracial; Gynera; Gynofen; Harmonette; Laurina; Liofora; Loette; Marvelon; Meliane; Mercilon; Microgynon; Minulet; Neogynon; Nordette; Nordiol; NuvaRing; Ovral; Tri-Minulet; Trigynera; Trinordiol; Triquilar; Yasmin; Yasminelle; YAZ; *Hong Kong*: Daphne; Diane; Eugynon†; Evra; Gracial; Gynera; Harmonet; Loette; Marvelon; Meliane; Mercilon; Microgynon; Nordette; Novynette; Rigevidon; Tri-Regol; Yasmin; YAZ; *Hung.*: Anteovin†; Belara; Cilest; Cyprommix; Diane; Dienille; Evra; Femoden; Gestomix; Gracial; Harmonet; Jangee; Laurina; Lindynette; Loette†; Marvelon; Meliane; Mercilon; Milligest; Minerva; Minesse†; Minulet; Novynette; NuvaRing; Ovidon†; Regulon; Rigevidon; Samba; Sensonette; Symicia; Tri-Regol; Trinordiol†; Triodena; Triquilar†; Volina; Yadine; Yasminelle; *India*: Choice; Combee; Crisanta; Dear-21; Diane; Dinac; Divacon; Dronis; Duoluton-L; Ergest; Femilon; Frauline; Ginette; Krimson; Locipil; Loette; Mixogen; Novelon; Ovilow; Ovimed; Ovipauz-L; Ovral; Triquilar; *Indon.*: Diane; Gynera; Marvelon; Mercilon; Microdiol; Microgynon; Pil Keluarga Berencana†; Planak; Trinordiol†; Triquilar; Yasmin; YAZ; *Irl.*: Brevinor†; Cilest; Dianette; Dretine; Dretinelle; Enador; Estelle; Evra; Gracial; Leonore; Leticia; Liofora; Logynon; Marviol; Mercilon; Microlite; Minesse; Minulet; NuvaRing; Ovogrel†; Ovran; Ovranette; Palandra; Rigevidon; Tri-Minulet; Trinordiol; Vivides; Vonodiol; Yasmin; Yasminelle; YAZ; *Israel*: Belara; Circlet; Diane; Emily; Estelle; Evra; Feminet; Flame; Floret; Gynera; Harmonet; Lodene; Meliane; Mercilon; Microdiol; Microgynon; Minesse; Minulet; Nordette; NuvaRing; Ortho Cyclen; Seasonique; Shelly; Yael; Yasmin; Yasminelle†; YAZ; *Ital.*: Arianna; Belara; Cirelet; Credigyne; Credigynette; Diane; Dueva; Egogyn; Estinette; Evra; Fedra; Femodette; Gestodiol; Ginoden; Gracial; Harmonet; Kipling; Loette; Lucille; Lybella; Mercilon; Microgynon; Midlana; Milvane; Minesse; Minigeste; Minulet; Miranova; Novogyn; Novynette; NuvaRing; Planum; Practil; Securgin; Tri-Minulet; Visofid; Yarina; Yasmin; Yasminelle; YAZ; *Jpn*: Ange; Lunabell; Ortho 777; *Malaysia*: Diane; Estelle; Evra; Gynera; Lindynette; Loette; Marvelon; Meliane; Mercilon; Microgynon 30; Minulet; Nordette; Novynette; NuvaRing; Oralcon; Regulon; Rigevidon; Sucee; Trigestrel; Trinordiol; Yasmin; YAZ; *Mex.*: Alesse; Angie; Belara; Cilest; Desmin; Detegen; Diane; Esdegen; Eunice 35-ED; Evra; Femexin; Ginelea; Gynovin; Letinnov; Marvelon; Mercilon; Microgynon; Mileva; Minesse; Minulet; Neogynon; Nordet; Nordiol†; Novial; NuvaRing; Ortho-Novum 1/35; Ovral; Radiance; Secret 28; Trinordiol; Triquilar; Yasmin; *Mon.*: Felixita; Leeloo; *Neth.*: Alesse†; Annantah; Armarrok; Armunia; Belanette; Cilest; Circlet; Diane; Evra; Femodeen; Gracial; Jamyle; Juliane; Laurina; Logynon†; Lonicera; Lovette; Marvelon; Mercilon; Microgynon; Minerva; Ministat; Minulet; Miranova; Modicon; Neocon; NuvaRing; Oralcon; Ovidol†; Palandra; Rosal; Stediril; Trigynon; Trinordiol; Trinovum; Vallciara; Volina; Yasmin; Yasminelle; YAZ; Yira†; Yvidually; Zypina†; *Norw.*: Diane; Evra; Feminil; Finminette; Loette; Marvelon; Mercilon; Microgynon; NuvaRing; Oralcon; Rubira; Synfase; Yasmin; Yasminelle; YAZ; Zyrona; *NZ*: Brevinor; Diane; Estelle; Femodene; Ginet; Levlen ED; Loette; Marvelon; Melodene†; Mercilon; Microgynon; Minulet; Monofeme; Nordette; Norimin; Roxanne; Synphasic; Trifeme; Triphasil; Triquilar; Yasmin; YAZ; *Philipp.*: Althea; Ancea; Azul; Blush; Charlize; Crimson; Diane; Evra; Femenal†; Femme; Gracial; Gynera; Lady; Logynon; Marvelon; Meliane; Mercilon; Microgynon†; Micropil Plus; Micropil; Minulet†; Nordette; Nordiol; Norfem; Rigevidon; Safe Pill; Seif; Trinordiol; Trust Pill; Yasmin; YAZ; *Pol.*: Aliane; Anteovin†; Artizia; Asubtela; Atywia; Chloe; Cilest; Circlet; Cyprest; Cyprodiol; Cyprogen; Diane; Dronin; Evra; Femipol; Femoden; Gravistat†; Harmonet; Jeanine; Kontracept; Linatera; Logest; Madinette; Marvelon; Mercilon; Microgynon; Midiana; Milvane; Minisiston†; Minulet†; Mirelle; Naraya; Novynette; NuvaRing; OC-35; Regulon; Rigevidon; Stediril; Sylvie; Syndi-35; Tri-Minulet†; Tri-Regol; Trinordiol; Trinovum†; Triquilar; Trisiston; Yasmin; Yasminelle; YAZ; *Port.*: Aliane; Belara; Diane; Effiplen; Estinette; Evra; Gracial; Gynera; Harmonet; Laurina; Libeli; Marvelon; Mercilon; Microgeste; Microginon; Minesse; Minigeste; Minulet; Miranova; Novynette; NuvaRing; Petibelle; Regulon; Tetragynon; Tri-Gynera; Tri-Minulet; Trinordiol; Triquilar†; Valette; Yasmin; Yasminelle; YAZ; *Rus.*: Anteovin (Антеовин)†; Belara (Белара); Bellune (Беллуне); Chloe (Хлое); Cilest (Силест); Diane (Диане); Evra (Евра); Femoden (Фемоден); Jeanine (Жанин); Lindynette (Линдинет); Logest (Логест); Marvelon (Марвелон); Mercilon (Мерсилон); Microgynon (Микрогинон); Minisiston (Миниситон); Non-Ovlon (Нововлон)†; Novynette (Новинет); NuvaRing (НоваРинг); Ovidon (Овидон)†; Regulon (Регулон); Rigevidon (Ригевидон); Tri-Merci (Три-Мерси); Tri-Regol (Три-Регол); Triquilar (Трикилар); Trisiston (Трисистон); Yarina (Ярина); YAZ (Джес); *S.Afr.*: Adco-Fem; Biphasil; Cilest; Claro; Diane; Diva; E-Gen-C; Evra; Femodene ED; Ginette; Harmonet†; Loette†; Logynon ED; Marvelon; Melodene; Menoflush; Mercilon; Minerva; Minesse; Minulette; Miranova†; Mirelle; Nordette; Nordiol; Ovral; Tri-Minulet†; TriCilest; Trinovum; Triodene; Triphasil; Yasmin; YAZ; *Singapore*: Diane; Estelle; Evra; Gynera; Loette†; Marvelon; Meliane; Mercilon; Microgynon; Minulet†; Nordette†; NuvaRing; Trinordiol†; Yasmin; YAZ; *Spain*: Ailyn; Antin; Antinelle; Aranka; Barianca; Belara; Bemasive; Danielle; Daylette; Diacare†; Dialider; Diane; Donabel; Drelle; Dretine; Dretinelle; Drosiane Diario; Drosianelle; Drospil; Drosure; Drosurelle; Edelsin; Eloine; Elynor; Evra; Gestinyl; Gracial; Gyneplen; Gynovin; Harmonet; Levobel; Liofora; Loette; Meliane; Melodene 15; Melteva; Microdiol; Microgynon; Minesse; Minulet; Neogynona; NuvaRing; Ovoplex; Regulon; Suavuret; Tevalet; Tri-Minulet; Triagynon; Triciclor; Trigynovin; Yasmin; Yasminelle; YAZ; Yira; *Swed.*: Abelonelle;

Cilest; Desolett; Diane; Eloine; Evra; Liofora; Mercilon; Neovletta; NuvaRing; Orthonett Novum; Prionelle; Restovar; Synfase; Trimiron†; Trinordiol; Trinovum; Trionetta; Triregol; Yasmin; Yasminelle; YAZ; Zyrona; *Switz.*: Belara; Belarina; Cilest; Cypestra; Cyprelle; Desoren; Diane; Eloine; Elyfem; Estinette; Evra; Femadiol; Feminac; Gestoden Plus; Gracial; Gynera; Gyselle; Harmonet; Holgyeme; Ladonna; Levomin; Liosanne; Madinette; Marvelon; Meliane; Meloden; Mercilon; Microgynon; Milvane; Minerva; Minesse; Minulet; Miranova; Mirelle; Myvlar; NuvaRing; Ologyn; Primosiston†; Trinovum; Tyarena; Yasmin; Yasminelle; YAZ; *Thai.*: Anna; Annie; Annylyn; B-Lady; Belara; Ciclomex; Cilest; Cypress; Dafne; Daisy; Diane; Dior; Evra; Gynera; Helen; Jeny-FMP; Lady-35; Lindynette; Manoane; Manodiol; Marvelon; Meliane; Melodia; Mercilon; Microgynon; Milvane; Minerva; Minesse; Minulet; Miranova; Mirelle; Myvlar; NuvaRing; Ologyn; Primosiston†; Trinovum; Tyarena; Yasmin; Yasminelle; YAZ; *Turk.*: Belara; Desolett; Diane; Ginera; Gynelle; Lo-Ovral; Lyndiol; Microgynon; Minulet; Miranova; Myralon; NuvaRing; Preven; Reginon; Triquilar†; Yasmin; Yazz; *UK*: Acnocin; Binovum; Brevinor; Cicafem; Cilest; Cimizz; Clairette; Dianette; Diva; Evra; Femodene; Femodette; Gedarel; Katya; Levest; Lizinna; Loestrin; Logynon; Marvelon; Mercilon; Microgynon 30; Millinette; Norimin; NuvaRing; Ovran 30; Ovranette; Ovysmen; Rigevidon; Sunya; Synphase; Triadene; Trinovum; Triregol; Yasmin; YAZ; *Ukr.*: Belara (Белара); Darilla (Дарилла); Diane-35 (Диане-35); Femoden (Фемоден); Jeanine (Жанин); Lindynette (Линдинет); Logest (Логест); Marvelon (Марвелон); Mercilon (Мерсилон); Microgynon (Микрогинон)†; Midiana (Мидиана); Novynette (Новинет); NuvaRing (НоваРинг); Ovidon (Овидон)†; Regulon (Регулон); Rigevidon (Ригевидон); Silhouette (Силует); Tri-Mercl (Три-Мерси); Tri-Regol (Три-Регол); Triquilar (Трикилар); Tristin (Тристин)†; Yarina (Ярина); *USA*: Alesse†; Altavera; Alyacen 1/35; Alyacen 7/7/7; Amethia; Apri; Aranelle; Aviane; Azurette; Balziva; Beyaz; Brevicon; Briellyn; Camrese; Caziant; Cesia; Chateal; Cryselle; Cyclessa; Daysee; Desogen; Enpresse; Estarylla; Estrostep Fe; Falmina; Femcon Fe; FemHRT; Gianvi; Jinteli; Jolessa; Junel Fe; Kariva; Kelnor; Kurvelo; Leena; Lessina; Levora; Lo Loestrin Fe; Lo Minastrin Fe; Lo/Ovral; Loestrin Fe; Loestrin; Loryna; LoSeasonique; Lutera; Lybrel; Marlissa; Minastrin 24 FE; Mircette; Modicon; Myzilra; Necon 10/11; Necon 0.5/35, 1/35; NEE 1/35; Nordette; Norinyl 1 + 35; Norrel; NuvaRing; Ocella; Ortho Cyclen; Ortho Evra; Ortho Tri-Cyclen; Ortho-Cept; Ortho-Novum 1/35; Ortho-Novum 10/11†; Ortho-Novum 7/7/7; Ovcon 35; Ovcon 50; Ovral†; Pirmella 1/35; Pirmella 7/7/7; Portia; Previfem; Quartette; Quasense; Reclipsen; Safyral; Seasonale; Seasonique; Solia; Sprintec; Sronyx; Syeda; Tilia Fe; Tri-Estarylla; Tri-Legest; Tri-Linyah; Tri-Lo-Sprintec; Tri-Norinyl; Tri-Previfem; Tri-Sprintec; TriNessa; Triphasil†; Trivora; Velivet; Vestura; Vioreie; Wymzya Fe; Yasmin; YAZ; Zarah; Zenchent Fe; Zenchent; Zovia; *Venez.*: Alesse; Belara; Ciclidon; Diane; Dixi; Evra; Femiane; Gynera; Harmonet; Marvelon; Mercilon; Minesse; Minigynon; Minulet; Mipil; Mirelle; Neogynon; Nordette; Nordiol; Novial; Orurel; Ovral; Rigevidon; Tri-Regol; Trinordiol; Triquilar; Yasmin.

Pharmacopoeial Preparations

BP 2014: Ethinylestradiol Tablets; Levonorgestrel and Ethinylestradiol Tablets;

USP 36: Desogestrel and Ethinyl Estradiol Tablets; Drospirenone and Ethinyl Estradiol Tablets; Ethinyl Estradiol Tablets; Ethynodiol Diacetate and Ethinyl Estradiol Tablets; Levonorgestrel and Ethinyl Estradiol Tablets; Norethindrone Acetate and Ethinyl Estradiol Tablets; Norethindrone and Ethinyl Estradiol Tablets; Norgestimate and Ethinyl Estradiol Tablets; Norgestrel and Ethinyl Estradiol Tablets.

Ethisterone *(BAN, rINN)*

Anhydrohydroxyprogesterone; Ethinyltestosterone; Ethisterone; Ethisteronum; Etisteron; Etisterona; Etisteroni; Etysteronum; NSC-9565; Praegninum; Pregneninolone; Pregnin. Этистерон.

17β-Hydroxy-17α-pregn-4-en-20-yn-3-one.

$C_{21}H_{28}O_2$=312.5

CAS — 434-03-7.

ATC — G03DC04.

ATC Vet — QG03DC04.

UNII — P2018V1IMU.

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Ethisterone is a progestogen that is structurally related to testosterone (p. 2305.1); it also has oestrogenic and androgenic properties. It is given orally with an oestrogen for the treatment of amenorrhoea (p. 2251.3). A dose of ethisterone 40 mg with ethinylestradiol 40 micrograms may be given twice daily for 3 days, and withdrawal bleeding occurs about 3 to 7 days later.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Ethylestrenol *(BAN, USAN, rINN)* ⊗

Ethylestrenol; Ethylestrenolum; Ethyloestrenol; Etilestrenol; Etylestrenol; Ethylestrenols. Этилестренол.

17α-Ethyl-4-en-17β-ol; 19-Nor-17α-pregn-4-en-17β-ol.

$C_{20}H_{32}O$=288.5

CAS — 965-90-2.

ATC — A14AB02.

ATC Vet — QA14AB02.

UNII — ADC79KSQ8.

Profile

Ethylestrenol is a 17α-alkylated anabolic steroid (see Testosterone, p. 2305.1) with little androgenic effect and slight progestogenic activity. It has been used for the promotion of growth in boys with short stature or delayed bone growth. It is used in veterinary medicine.

Etonogestrel *(BAN, USAN, rINN)*

Etonogestreel; Etonogestrel; Etonogestrelum; 3-keto-Desogestrel; Org-3236; Этоногестрел.

13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one; 17β-Hydroxy-11-methylene-18-homo-19-nor-17α-pregn-4-en-20-yn-3-one.

$C_{22}H_{28}O_2$=324.5

CAS — 54048-10-1.

ATC — G03AC08.

ATC Vet — QG03AC08.

UNII — 304GTH6RNH.

Uses and Administration

Etonogestrel, the active metabolite of desogestrel (p. 2266.3), is used as a hormonal contraceptive (see p. 2231.3). A subdermal implant containing 68 mg of etonogestrel is used as a progestogen-only contraceptive that is effective for 3 years. Etonogestrel is also used as the progestogen component of a combined contraceptive delivered via a vaginal ring device. The ring releases an average of 120 micrograms daily of etonogestrel and 15 micrograms daily of ethinylestradiol and remains in the vagina for 3 weeks; it is then removed for a one-week break after which a new ring is inserted.

Etonogestrel is under investigation as a male contraceptive, given orally or by implant, with testosterone implants or injections.

References.

1. Edwards JB, Moore A. Implanon: a review of clinical studies. *Br J Fam Plann* 1999; 24: 3–16.
2. Le J, Tsourounis C. Implanon: a critical review. *Ann Pharmacother* 2001; 35: 329–36.
3. Roumen F. Contraceptive efficacy and tolerability with a novel combined contraceptive vaginal ring, NuvaRing. *Eur J Contracept Reprod Health Care* 2002; 7 (suppl 2): 19–24.
4. Meirik O, *et al.* WHO Consultation on Implantable Contraceptives for Women. Implantable contraceptives for women. *Hum Reprod Update* 2003; 9: 49–59.
5. Sarkar NN. The combined contraceptive vaginal device (NuvaRing): a comprehensive review. *Eur J Contracept Reprod Health Care* 2005; 10: 73–8.
6. Roumen FJ. The contraceptive vaginal ring compared with the combined oral contraceptive pill: a comprehensive review of randomized controlled trials. *Contraception* 2007; 75: 420–9.
7. Mommers E, *et al.* Male hormonal contraception: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2008; 93: 2572–80.
8. Adams K, Beal MW. Implanon: a review of the literature with recommendations for clinical management. *J Midwifery Womens Health* 2009; 54: 142–9.
9. Barreiros FA, *et al.* Extended regimens of the contraceptive vaginal ring: evaluation of clinical aspects. *Contraception* 2010; 81: 223–5.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Breast feeding. Etonogestrel was found in the breast milk of 42 women given a contraceptive etonogestrel implant. Over the 4-month study, compared with a group who used an intra-uterine non-hormonal device, etonogestrel did not affect the volume or composition of breast milk, or the growth of the breast-fed infants.[1] At 3 years of age there was no difference in growth between these 2 groups of children.[2]

1. Reinprayoon D, *et al.* Effects of the etonogestrel-releasing contraceptive implant (Implanon) on parameters of breastfeeding compared to those of an intrauterine device. *Contraception* 2000; 62: 239–46.
2. Tanvetpanichskul S, *et al.* Effects of the etonogestrel-releasing implant Implanon and a nonmedicated intrauterine device on the growth of breast-fed infants. *Contraception* 2006; 73: 368–71.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etonogestrel 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 04/10/11)

Vaginal bleeding. Prolonged vaginal bleeding, lasting from 2 to 26 weeks, has been reported with the use of etonogestrel subdermal implants. Blood transfusion was needed in the management of one patient.[1] Mifepristone, combined with either ethinylestradiol or doxycycline has also proved effective in terminating bleeding episodes caused by etonogestrel.[2] Heavy bleeding has been described in 2 women after the implant had broken while in place.[3,4]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Implanon and vaginal bleeding. *Aust Adverse Drug React Bull* 2003; 22: 11–12. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0306.pdf (accessed 27/06/08)
2. Weisberg E, *et al.* A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users. *Hum Reprod* 2009; 24: 1852–61.
3. Pickard S, Bacon L. Persistent vaginal bleeding in a patient with a broken Implanon. *J Fam Plann Reprod Health Care* 2002; 28: 207–8.
4. Agrawal A, Robinson C. Spontaneous snapping of an Implanon in two halves in situ. *J Fam Plann Reprod Health Care* 2003; 29: 238.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

Etonogestrel is highly bound to plasma proteins; about 32% is bound to sex hormone binding globulin and 66% to albumin. It is metabolised by the cytochrome P450 isoenzyme CYP3A4, and both metabolites and unchanged drug are excreted in the urine and faeces. The elimination half-life is about 25 to 30 hours. Etonogestrel is distributed into breast milk.

References.

1. Timmer CJ, Mulders TMT. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. *Clin Pharmacokinet* 2000; 39: 233–42.
2. Bennink HJ. The pharmacokinetics and pharmacodynamics of Implanon, a single-rod etonogestrel contraceptive implant. *Eur J Contracept Reprod Health Care* 2000; 5 (suppl 2): 12–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Implanon; *Austria*: Implanon; *Belg.*: Implanon; *Braz.*: Implanon; *Chile*: Implanon; *China*: Implanon (依伴侬); *Cz.*: Implanon; *Denm.*: Implanon; Nexplanon; *Fin.*: Implanon†; Nexplanon; *Fr.*: Implanon†; Nexplanon; *Ger.*: Implanon; *Gr.*: Implanon; *Hung.*: Implanon; *Indon.*: Implanon; *Irl.*: Implanon; *Malaysia*: Implanon; *Mex.*: Implanon; *Neth.*: Implanon; *Norw.*: Implanon†; Nexplanon; *NZ*: Implanon; *Port.*: Implanon; *Singapore*: Implanon; *Spain*: Implanon; *Swed.*: Implanon†; Nexplanon; *Switz.*: Implanon; *Thai.*: Implanon; NuvaRing; *Turk.*: Implanon; *UK*: Implanon†; Nexplanon; *USA*: Implanon; Nexplanon; *Venez.*: Implanon.

Multi-ingredient Preparations. *Austral.*: NuvaRing; *Austria*: NuvaRing; *Belg.*: NuvaRing; *Braz.*: NuvaRing; *Canad.*: NuvaRing; *Chile*: NuvaRing; *Cz.*: Circlet; NuvaRing; *Denm.*: NuvaRing; *Fin.*: NuvaRing; *Fr.*: NuvaRing; *Ger.*: NuvaRing; *Gr.*: NuvaRing; *Hung.*: NuvaRing; *Irl.*: NuvaRing; *Israel*: Circlet; NuvaRing; *Ital.*: Circlet; NuvaRing; *Malaysia*: NuvaRing; *Mex.*: NuvaRing; *Neth.*: Circlet; NuvaRing; *Norw.*: NuvaRing; *Pol.*: Circlet; NuvaRing; *Port.*: NuvaRing; *Rus.*: NuvaRing (НоваРинг); *Singapore*: NuvaRing; *Spain*: NuvaRing; *Swed.*: NuvaRing; *Switz.*: NuvaRing; *Turk.*: NuvaRing; *UK*: NuvaRing; *Ukr.*: NuvaRing (НоваРинг); *USA*: NuvaRing.

Etynodiol Diacetate *(BANM, pINNM)*

Aethynodiolum Diaceticum; Diacetato de etinodiol; Ethynodiol Diacetate (USAN); Etinodiol diacetato de; Etynodiol Diacetate d'; Etynodiol Diacetas; SC-1800; Этинодиола Диацетат.

19-Nor-17α-pregn-4-en-20-yne-3β,17β-diol diacetate.

$C_{24}H_{32}O_4$=384.5

CAS — 1231-93-2 (etynodiol); 297-76-7 (etynodiol diacetate).

ATC — G03DC06.

ATC Vet — QG03DC06.

UNII — 62H10A1236.

Pharmacopoeias. In *Br.*, *Pol.*, and *US*.

BP 2014: (Etynodiol Diacetate). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol; freely soluble in chloroform and in ether. Protect from light.

USP 36: (Ethynodiol Diacetate). A white, odourless, crystalline powder. Insoluble in water; soluble in alcohol; very soluble in chloroform; freely soluble in ether; sparingly soluble in fixed oils. Protect from light.

Uses and Administration

Etynodiol diacetate is a progestogen (see Progesterone, p. 2300.2) that is used as the progestogenic component of combined oral contraceptives and also alone as an oral progestogen-only contraceptive (see p. 2231.3); typical daily doses are 1 or 2 mg in combination products and 500 micrograms for progestogen-only contraceptives.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Pregnancy. Fetal adrenal cytomegaly in a 17-week-old fetus was associated with the maternal ingestion of an oral contraceptive containing etynodiol diacetate 2 mg and mestranol 100 micrograms from the sixth to the fourteenth week of pregnancy.[1]

1. Gau GS, Bennett MJ. Fetal adrenal cytomegaly. *J Clin Pathol* 1979; 32: 305–6.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

Etynodiol diacetate is readily absorbed from the gastrointestinal tract and rapidly metabolised, largely to norethisterone (p. 2294.2). About 60% of a dose is stated to be excreted in urine and about 30% in faeces; the half-life in plasma is about 25 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *NZ:* Femulen†; *UK:* Femulen†.

Multi-ingredient Preparations. *Arg.:* Soluna; *Canad.:* Demulen; *USA:* Kelnor; Zovia.

Pharmacopoeial Preparations
USP 36: Ethynodiol Diacetate and Ethinyl Estradiol Tablets; Ethynodiol Diacetate and Mestranol Tablets.

Flugestone Acetate *(BANM, rINNM)*

Acetato de flugestona; Flugestona, acetato de; Flugestone, Acétate de; Flugestoni Acetas; Flurogestone Acetate (USAN); NSC-65411; SC-9880; Флугестона Ацетат.

9α-Fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione 17-acetate.

$C_{23}H_{31}FO_5$=406.5

CAS — 337-03-1 (flugestone); 2529-45-5 (flugestone acetate).

UNII — X60881643X.

Profile

Flugestone acetate is a progestogen (see Progesterone, p. 2300.2) used in veterinary medicine.

Fluoxymesterone *(BAN, rINN)* ⊗

Fluoksimesteroni; Fluoximesteron; Fluoximesterona; Fluoxymestérone; Fluoxymesteronum; Fluximesterona; NSC-12165; Флуоксиместерон.

9α-Fluoro-11β,17β-dihydroxy-17α-methylandrost-4-en-3-one.

$C_{20}H_{29}FO_3$=336.4

CAS — 76-43-7.

ATC — G03BA01.

ATC Vet — QG03BA01.

UNII — 9JU12S4YFY.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Fluoxymesterone). A white or practically white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform. Protect from light.

Uses and Administration

Fluoxymesterone has androgenic properties (see Testosterone, p. 2305.2). It is effective when given orally and is more potent than methyltestosterone.

In the treatment of male hypogonadism (p. 2252.3), fluoxymesterone has been given in a dosage of 5 to 20 mg daily. For the use of fluoxymesterone in boys with delayed puberty, see Administration in Children, below. In the palliation of inoperable neoplasms of the breast in postmenopausal women (p. 702.1) it has been given in doses of 10 to 40 mg daily, in divided doses. Fluoxymesterone has also been used in the treatment of aplastic anaemia.

Administration in children. In the treatment of delayed puberty (p. 2252.1) in boys, fluoxymesterone has been given orally in usual daily doses of 2.5 to 10 mg, adjusted according to response (doses up to 20 mg daily have been used). Care is necessary because of the risk of epiphyseal closure and treatment is generally only given for 4 to 6 months.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

As with other 17α-alkylated compounds fluoxymesterone may cause hepatotoxicity, and is probably best avoided in patients with hepatic impairment, and certainly if this is severe... Hepatic function should be monitored during therapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.:* Halotestin; *Mex.:* Stenox; *USA:* Androxy.

Multi-ingredient Preparations. *Arg.:* Ferona†.

Pharmacopoeial Preparations
USP 36: Fluoxymesterone Tablets.

Follicle-stimulating Hormone

Folitrofina; Folitropina; FSH; Gonadotrofina foliculoestimulante; Hormona estimulante del folículo.

ATC Vet — QG03GA90.

UNII — 8W9AS43IDH (follicle stimulating hormone beta polypeptide).

Pharmacopoeias. *Eur.* (see p. vii) includes Follitropin and Follitropin Concentrated Solution.

Follitropin Alfa *(BAN, rINN)*

Folitrofina alfa; Folitropin Alfa; Folitropina alfa; Follitropine Alfa; Follitropinum Alfa; Фоллитропин Альфа.

$C_{437}H_{682}N_{122}O_{134}S_{13}$ = 10206 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ = 12485 (β-subunit)

CAS — 9002-68-0 (follitropin alfa); 56832-30-5 (α-subunit); 110909-60-9 (β-subunit); 146479-72-3 (follitropin alfa).

ATC — G03GA05.

ATC Vet — QG03GA05.

UNII — 076WHW89TW.

Follitropin Beta *(BAN, rINN)*

Folitrofina beta; Folitropin Beta; Folitropina beta; Follitropine Bêta; Follitropinum Beta; Org-32489; Фоллитропин Бета.

$C_{437}H_{682}N_{122}O_{134}S_{13}$ = 10206 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ = 12485 (β-subunit)

CAS — 169108-34-3 (follitropin beta); 150490-84-9 (follitropin beta); 56832-30-5 (α-subunit); 110909-60-9 (β-subunit).

ATC — G03GA06.

ATC Vet — QG03GA06.

Units

80 units of human pituitary follicle-stimulating hormone are contained in about 4.17 micrograms (with 5 mg of mannitol and 1 mg human serum albumin) in one ampoule of the first International Standard (1986).

138 units of recombinant human follicle-stimulating hormone for bioassay are contained in one ampoule of the first International Standard (1995).

Uses and Administration

Follicle-stimulating hormone is secreted by the anterior lobe of the pituitary gland, with another gonadotrophin, luteinising hormone (p. 2287.1).

These gonadotrophins stimulate the normal functioning of the gonads and the secretion of sex hormones in both men and women. In women, follicle-stimulating hormone stimulates the development and maturation of the follicles and ova; in men it has a role in spermatogenesis.

Recombinant human follicle-stimulating hormones (follitropins alfa or beta) are used in the treatment of female infertility due to anovulation, in women who have not responded to clomifene therapy. Follitropins are also used for the stimulation of spermatogenesis in the management of male infertility caused by hypogonadotrophic hypogonadism (see Infertility, p. 2253.1).

The dosage and schedule of treatment for **female infertility** must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles or both. In menstruating patients treatment should be started within the first 7 days of the menstrual cycle.

- Treatment is usually begun with 75 to 150 units daily by subcutaneous or intramuscular injection for 7 or 14 days; if there is no response, dosage is increased at 7- or 14-day intervals until an adequate but not excessive response is achieved.
- Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units to induce ovulation.

It has been suggested in UK licensed product information for follitropin alfa that a daily dose of 225 units is the usual maximum, and that if a patient fails to respond adequately after 4 weeks of treatment that cycle should be abandoned and the patient should subsequently begin the next cycle at a higher starting dose.

Follitropins are also used as part of IVF or other assisted reproductive technologies.

- For this purpose doses of 150 to 225 units daily are generally given, for at least 4 days, starting on the second or third day of the menstrual cycle. Thereafter the dose may be adjusted individually based on ovarian response to a usual maximum of about 450 units; adequate follicular development generally occurs within about 5 to 10 days of treatment.
- Pituitary downregulation with a gonadorelin analogue may be used with follitropin therapy, in which case the gonadorelin analogue is generally begun about 2 weeks before follitropin, and the 2 are then continued together until follicular development is adequate.
- A single dose of up to 10 000 units of chorionic gonadotrophin is then given to induce final follicular maturation and oocyte retrieval performed about 35 hours later.

Follitropins are used for the stimulation of spermatogenesis in the management of **male infertility** caused by hypogonadotrophic hypogonadism. Before starting follitropin therapy, chorionic gonadotrophin is given to raise serum testosterone concentrations to the normal range, which may take 3 to 6 months. A dose of follitropin alfa or beta of 150 units subcutaneously three times weekly is then used, with continued chorionic gonadotrophin; doses of follitropin alfa up to 300 units three times weekly may be required. Treatment is continued for at least 4 months, and more than 18 months of treatment may be needed. A dose of follitropin beta 75 units daily or two or three times weekly, by subcutaneous or intramuscular injection, has been used similarly.

Other substances with follicle-stimulating activity are used similarly: these include human menopausal gonadotrophins (p. 2284.1), which have both luteinising and follicle-stimulating activity, and urofollitropin (p. 2312.2).

Infertility. For a suggestion that human menopausal gonadotrophins may be associated with higher live-birth rates than recombinant follicle-stimulating hormone when used in current IVF protocols, see p. 2284.2.

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p. 2284.3. Varicocele has occurred in men treated with follitropin alfa.

Spongiform encephalopathies. In a few countries, gonadotrophins derived from cadaver pituitary glands have been used in the treatment of infertility, and a small number of patients are reported to have acquired Creutzfeldt-Jakob disease from such preparations.[1] However, most countries have preferred to use gonadotrophins derived from urine,[1] and these in their turn are being replaced with recombinant products;[2] such preparations appear to carry negligible risk of transmitting prion disease.[3-5]

1. Healy DL, Evans J. Creutzfeldt-Jakob disease after pituitary gonadotrophins. *BMJ* 1993; 307: 517–18.
2. Eshkol A, Page ML. Human gonadotrophin preparations. *BMJ* 1994; 308: 789.
3. Matorras R, Rodríguez-Escudero FJ. Bye-bye urinary gonadotrophins? The use of urinary gonadotrophins should be discouraged. *Hum Reprod* 2002; 17: 1675.
4. Balen A. Is there a risk of prion disease after the administration of urinary-derived gonadotrophins? *Hum Reprod* 2002; 17: 1676–80.
5. Jansen C. Bye-bye urinary gonadotrophins? Reply to debate. *Hum Reprod* 2003; 18: 895–6.

Pharmacokinetics

Follitropins alfa and beta are slowly absorbed after subcutaneous or intramuscular injection, with an absolute bioavailability of about 70 to 80%. Peak plasma concentrations of follitropin beta have occurred about 12 hours after subcutaneous or intramuscular injection. Accumulation occurs with repeated doses, reaching a steady state within 3 to 5 days. Follitropins are slowly eliminated from the body, with a terminal half-life ranging from 12 to 70 hours. About one-eighth of a dose of follitropin alfa is reported to be excreted in the urine.

References.

1. Karlsson MO, *et al.* The population pharmacokinetics of recombinant- and urinary-human follicle stimulating hormone in women. *Br J Clin Pharmacol* 1998; 45: 13–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gonal-F; Puregon; *Austral.*: Gonal-F; Puregon; *Austria*: Gonal-F; Puregon; *Belg.*: Gonal-F; Puregon; *Braz.*: Gonal-F; Puregon; *Canad.*: Gonal-F; Puregon; *Chile*: Gonal-F; Puregon; *China*: Gonal-F (果纳芬); Puregon (普丽康); *Cz.*: Fertavid; Gonal-F; Puregon; *Denm.*: Gonal-F; Puregon; *Fin.*: Gonal-F; Puregon; *Fr.*: Gonal-F; Puregon; *Ger.*: Gonal-F; Puregon; *Gr.*: Gonal-F; Puregon; *Hong Kong*: Gonal-F; Puregon; *Hung.*: Gonal-F; Puregon; *India*: Folligrat; Gonal-F; Nisfollic; *Indon.*: Gonal-F; Puregon; *Irl.*: Fertavid; Gonal-F; Puregon; *Israel*: Gonal-F; Puregon; *Ital.*: Gonal-F; Puregon; *Malaysia*: Gonal-F; Puregon; *Mex.*: Gonal-F†; Puregon; *Neth.*: Fertavid; Gonal-F; Puregon; *Norw.*: Gonal-F; Puregon; *NZ*: Gonal-F; Puregon; *Philipp.*: Gonal-F; Puregon; *Pol.*: Fertavid; Gonal-F; Puregon; *Port.*: Fertavid; Gonal-F; Puregon; *Rus.*: Follitrop (ФОЛЛИТРОП); Gonal-F (Гонал-Ф); Puregon (Пуреон); *S.Afr.*: Gonal-F; *Singapore*: Gonal-F; Puregon; *Spain*: Gonal-F; Puregon; *Swed.*: Gonal-F; Puregon; *Switz.*: Fertelle; Gonal-F; Puregon; *Thai.*: Gonal-F; Puregon; *Turk.*: Gonal-F; Puregon; *UK*: Gonal-F; Puregon; *Ukr.*: Puregon (Пуреон); *USA*: Follistim; Gonal-F; *Venez.*: Gonal-F; Puregon.

Multi-ingredient Preparations. *Arg.*: Pergoveris; *Austria*: Pergoveris; *Belg.*: Pergoveris; *Braz.*: Pergoveris; *Cz.*: Pergoveris; *Denm.*: Pergoveris; *Fr.*: Pergoveris; *Ger.*: Pergoveris; *Gr.*: Pergoveris; *Hung.*: Pergoveris; *Irl.*: Pergoveris; *Israel*: Pergoveris; *Ital.*: Pergoveris; *Neth.*: Pergoveris; *Norw.*: Pergoveris; *Pol.*: Pergoveris; *Port.*: Pergoveris; *Rus.*: HuMoG (ХуМоГ); *Singapore*: Pergoveris; *Spain*: Pergoveris; *Swed.*: Pergoveris†; *Switz.*: Pergoveris; *UK*: Pergoveris.

Formebolone *(BAN, rINN)* ⊗

Formebolona; Formébolone; Formebolonum; Formyldienolone; Формеболон.

11α,17β-Dihydroxy-17β-methyl-3-oxoandrosta-1,4-diene-2-carbaldehyde.

$C_{21}H_{28}O_4$=344.5

CAS — 2454-11-7

UNII — Z2MMV08KUQ

Profile

Formebolone has been used for its anabolic properties (see Testosterone, p. 2305.1). It appears to be widely abused by body-builders.

Fosfestrol *(BAN, rINN)*

Diethylstilbestrol Diphosphate; Fosfestroli; Fosfestrolum; Phosphoestrolum; Stilboestrol Diphosphate; Фосфестрол.

(*E*)-α,α'-Diethylstilbene-4,4'-diol bis(dihydrogen phosphate); (*E*)-4,4'-(1,2-Diethylvinylene)bis(phenyl dihydrogen orthophosphate).

$C_{18}H_{22}O_8P_2$=428.3

CAS — 522-40-7.

ATC — L02AA04.

ATC Vet — QL02AA04.

UNII — A0E0NMA80F.

Pharmacopoeias. In *Jpn.*

Fosfestrol Sodium *(BANM, rINNM)*

Fosfestrol sódico; Fosfestrol Sodique; Natrii Fosfestrolum; Натрий Фосфестрол.

$C_{18}H_{18}Na_4O_8P_2$=516.2

CAS — 23519-26-8 (fosfestrol tetrasodium xH_2O); 4719-75-9 (anhydrous fosfestrol tetrasodium).

ATC — L02AA04.

ATC Vet — QL02AA04.

UNII — G911882VSD.

Pharmacopoeias. In *Br.*, which specifies xH_2O.

BP 2014: (Fosfestrol Sodium). A white or almost white powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in ether. A 5% solution in water has a pH of 7.0 to 9.0. Protect from light.

Uses and Administration

Fosfestrol is a synthetic nonsteroidal oestrogen that requires dephosphorylation to diethylstilbestrol (p. 2267.3) before it is active. It is used in the treatment of malignant neoplasms of the prostate (p. 712.3).

Fosfestrol and its sodium salt have both been used, and doses of fosfestrol sodium may be expressed in terms of either the base or the salt; anhydrous fosfestrol sodium 300 mg is equivalent to about 250 mg of fosfestrol. Expressed in terms of fosfestrol sodium, initial doses of 600 to 1200 mg daily by slow intravenous injection over about 1 hour may be given for 5 to 10 days, followed by 300 mg daily for 10 to 20 days. Injections should be given preferably with the patient lying down. Maintenance intravenous doses of fosfestrol sodium 300 to 600 mg may be given, reduced gradually over several months from dosing 4 times a week to once weekly. Fosfestrol sodium may also be given orally. If initial doses cannot be given intravenously, doses of 360 to 480 mg three times daily have been given orally. For maintenance therapy, doses of 120 to 240 mg three times daily may be used, and gradually reduced to 240 mg daily.

Adverse Effects and Precautions

As for Diethylstilbestrol, see p. 2268.1.

After intravenous injection of fosfestrol sodium there may be a temporary burning sensation in the perineal region and pain at the site of bony metastases. Slow infusion is not recommended as cytotoxic concentrations of the drug may not be achieved.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Honvol†; *Gr.*: Honvan; *India*: Honvan.

Pharmacopoeial Preparations

BP 2014: Fosfestrol Injection; Fosfestrol Tablets.

Ganirelix Acetate *(BANM, USAN, rINNM)*

Acetato de ganirelix; Ganirelix, Acétate de; Ganirelix, acetato de; Ganirelixi Acetas; Org-37462; RS-26306; Ганиреликса Ацетат.

N-Acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-*N*^{6}-(*N*,*N*-diethylamidino)-D-lysyl-L-leucyl-*N*^{6}-(*N*,*N*-diethylamidino)-L-lysyl-L-prolyl-D-alaninamide acetate.

$C_{80}H_{113}ClN_{18}O_{13}.2C_2H_4O_2$=1690.5

CAS — 124904-93-4 (ganirelix); 129311-55-3 (ganirelix acetate).

ATC — H01CC01.

ATC Vet — QH01CC01.

UNII — 56U7906FQW.

Uses and Administration

Like cetrorelix (p. 2257.2), ganirelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is given to prevent premature luteinising hormone surges that can occur during controlled ovarian stimulation, which is a component of assisted reproduction used in infertility (p. 2253.1). Doses are expressed in terms of the acetate or the equivalent amount of base. Ganirelix acetate 108 mg is equivalent to about 100 mg of ganirelix. In the UK a dose equivalent to ganirelix 250 micrograms is given by subcutaneous injection once daily, starting on day 5 or 6 of ovarian stimulation and continued until ovulation induction. In the USA a dose of ganirelix acetate 250 micrograms is used similarly.

References.

1. Gillies PS, *et al.* Ganirelix. *Drugs* 2000; 59: 107–11.
2. The European Orgalutran Study Group, *et al.* Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. *Hum Reprod* 2000; 15: 1490–8. Correction. *ibid.*: 1877.
3. The North American Ganirelix Study Group. Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation. *Fertil Steril* 2001; 75: 38–45.
4. European and Middle East Orgalutran Study Group. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation. *Hum Reprod* 2001; 16: 644–51.
5. Griesinger G, *et al.* Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differences between agents? *Drugs* 2004; 64: 563–75.
6. Out HJ, *et al.* A randomized, double-blind, multicentre clinical trial comparing starting doses of 150 and 200 IU of recombinant FSH in women treated with the GnRH antagonist ganirelix for assisted reproduction. *Hum Reprod* 2004; 19: 90–5.
7. Wilcox J, *et al.* CAP IV Investigator Group. Prospective, randomized trial comparing cetrorelix acetate and ganirelix acetate in a programmed, flexible protocol for premature luteinizing hormone surge prevention in assisted reproductive technologies. *Fertil Steril* 2005; 84: 108–17.
8. Lambalk CB, *et al.* Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinization in stimulated intrauterine insemination: results of a double-blind, placebo-controlled, multicentre trial. *Hum Reprod* 2006; 21: 632–9.

Adverse Effects and Precautions

As for Cetrorelix, p. 2257.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ganirelix 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 06/10/11)

Pharmacokinetics

Ganirelix is rapidly absorbed after subcutaneous injection, with a bioavailability of about 91%. It is metabolised by enzymatic hydrolysis and about 75% of a dose is excreted as metabolites in the faeces. Unchanged drug is found in the urine. The elimination half-life of ganirelix is about 13 hours.

References.

1. Oberyé JJL, *et al.* Pharmacokinetic and pharmacodynamic characteristics of ganirelix (Antagon/Orgalutron) part I: absolute bioavailability of 0.25 mg of ganirelix after a single subcutaneous injection in healthy female volunteers. *Fertil Steril* 1999; 72: 1001–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Orgalutran; *Austral.*: Orgalutran; *Austria*: Orgalutran; *Belg.*: Orgalutran; *Braz.*: Orgalutran; *Canad.*: Orgalutran; *Chile*: Orgalutran; *Cz.*: Orgalutran; *Denm.*: Orgalutran; *Fin.*: Orgalutran; *Fr.*: Orgalutran; *Ger.*: Orgalutran; *Gr.*: Orgalutran; *Hong Kong*: Orgalutran; *Hung.*: Orgalutran; *India*: Orgalutran; *Indon.*: Orgalutran; *Irl.*: Orgalutran; *Israel*: Orgalutran; *Ital.*: Orgalutran; *Malaysia*: Orgalutran; *Mex.*: Orgalutran; *Neth.*: Orgalutran; *Norw.*: Orgalutran; *NZ*: Orgalutran; *Philipp.*: Orgalutran†; *Pol.*: Orgalutran; *Port.*: Orgalutran; *Rus.*: Orgalutran (Оргалутран); *Singapore*: Orgalutran; *Spain*: Orgalutran; *Swed.*: Orgalutran; *Switz.*: Orgalutran; *Thai.*: Orgalutran; *Turk.*: Orgalutran; *UK*: Orgalutran; *Ukr.*: Orgalutran (Оргалутран); *Venez.*: Orgalutran.

Gestodene *(BAN, USAN, rINN)*

Gestodeeni; Gestoden; Gestodène; Gestodeno; Gestodenum; SH-B-331; Гестоден.

13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one.

$C_{21}H_{26}O_2$=310.4

CAS — 60282-87-3.

UNII — 1664P6E6ML.

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

Ph. Eur. 8: (Gestodene). A white or yellowish, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in dichloromethane.

Uses and Administration

Gestodene is a progestogen (see Progesterone, p. 2300.2) structurally related to levonorgestrel. It is used as the progestogenic component of combined oral contraceptives (see p. 2231.3); a typical daily dose is 75 micrograms in monophasic preparations, and 50 to 100 micrograms in triphasic preparations. Gestodene is also used orally as the progestogenic component of menopausal HRT (see p. 2244.2) in a regimen of 25 or 50 micrograms daily for 12 days of a 28-day cycle.

Reviews.

1. Anonymous. Femodene/Minulet—how different is gestodene? *Drug Ther Bull* 1990; 28: 41–2.
2. Wilde MI, Balfour JA. Gestodene: a review of its pharmacology, efficacy and tolerability in combined contraceptive preparations. *Drugs* 1995; 50: 364–95.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3. Gestodene is reported to have few androgenic effects, and to have less adverse effect on the serum lipid profile than older 19-nortestosterone derivatives. However, there is some evidence that gestodene-containing combined oral contraceptives are associated with a small increased risk of venous thromboembolism (see p. 2238.1, and for precautions, see under Cardiovascular Disease, p. 2241.2).

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Antiepileptics. *Felbamate* significantly increased gestodene clearance from a low-dose combined oral contraceptive, and might decrease contraceptive efficacy.[1] See also p. 2243.2.

1. Saano V, *et al.* Effects of felbamate on the pharmacokinetics of a low-dose combination oral contraceptive. *Clin Pharmacol Ther* 1995; 58: 523–31.

Pharmacokinetics

Gestodene is well absorbed with a high bioavailability when given orally. It is extensively bound to plasma proteins; 75 to 87% to sex hormone binding globulin, and 13 to 24% to albumin. Gestodene is metabolised in the liver, less than 1% of a dose being excreted in the urine unchanged. After

multiple doses with ethinylestradiol, gestodene has an elimination half-life of about 20 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Aleli; Biofem; Cuidafem; Femiane; Ginelea T; Ginelea; Gynovin; Harmonet; Livianne; Mesconcept†; Minesse; Minulet; Mirelle; Secret 28; Venisse; *Austral.*: Femoden ED†; Minulet; Triodent†; *Austria*: Gynovin; Harmonette; Lenea; Meliane; Minesse; Minulet; Mirelle; Sylgestrel; Triodena; Wave; Yris; *Belg.*: Femodene; Gestodelle; Gestofeme; Harmonet; Meliane; Minulet; Mirelle; Mylenamylan†; Tri-Minulet; Triodene; *Braz.*: Adoless; Alexa; Allestra; Avaden; Ciclogyn; Diminut; Femiane; Fertnon; Gestinol; Ginesse; Gynera; Harmonet; Lizzy; Micropil; Minesse; Minima; Minulet; Mirelle; Previane; Siblima; Tamisa; Tantin; *Chile*: Avadent; Careza; Ciclomex; Feminol; Gynera; Harmonet; Microgen; Minesse; Minigest; Minulet; Mirelle; Tri-Ciclomex†; *China*: Minulet (敏定偶); *Cz.*: Artizia; Femoden; Harmonet; Katya; Lindynette; Logest; Lunafem; Milligest; Minesse; Minulet; Mirelle; Nelya; Stodette; Sunya; Tri-Minulet; *Denm.*: Estinette; Gestinyl; Gestodilat; Gestonette; Harmonet; Lindynette; Milligest; Milna; Milvane; Minero; Minulet; Modina; Vellena; *Fin.*: Femoden; Gestinyl; Gestodilat; Harmonet; Meliane; Minero; Minulet; Mirelle; Modina; Tri-Femoden; *Fr.*: Avadene; Carlin; Edenelle; Efezial; Harmonet; Meliane; Melodia; Minesse; Minulet; Moneva; Optinesse; Perleane; Phaeva; Sylviane; Tri-Minulet; *Ger.*: Femovan; Minulet; *Gr.*: Gynera; Harmonette; Meliane; Minulet; Tri-Minulet; Trigynera; *Hong Kong*: Gynera; Harmonet; Meliane; *Hung.*: Femoden; Gestomix; Harmonet; Lindynette; Meliane; Milligest; Minesse†; Minulet; Sensonette; Triodena; *Indon.*: Gynera; *Irl.*: Estelle; Minesse; Minulet; Tri-Minulet; *Israel*: Emily; Flame; Floret; Gynera; Harmonet; Lodene; Meliane; Minesse; Minulet; Shelly; Yael; *Ital.*: Arianna; Estinette; Fedra; Femodette; Gestodiol; Ginoden; Harmonet; Kipling; Milvane; Minesse; Minigeste; Minulet; Tri-Minulet; *Malaysia*: Gynera; Lindynette; Meliane; Minulet; *Mex.*: Avaden; Ginelea; Gynovin; Minesse; Minulet; Secret 28; *Mon.*: Felixita; *Neth.*: Annantah; Femodeen; Jamyle; Minulet; *NZ*: Femodene; Melodene†; Minulet; *Philipp.*: Gynera; Meliane; Minulet†; *Pol.*: Artizia; Femipol; Femoden; Harmonet; Kontracept; Logest; Milvane; Minulet†; Mirelle; Sylvie; Tri-Minulet†; *Port.*: Avadene; Effiplen; Estinette; Gynera; Harmonet; Microgeste; Minesse; Minigeste; Minulet; Tri-Gynera; Tri-Minulet; *Rus.*: Femoden (Фемоден); Lindynette (Линдинет); Logest (Логест); *S.Afr.*: Femodene ED; Harmonet†; Melodene; Minesse; Minulette; Mirelle; Tri-Minulet†; Triodene; *Singapore*: Gynera; Meliane; Minulet†; *Spain*: Gestinyl; Gynovin; Harmonet; Meliane; Melodene 15; Melteva; Minesse; Minulet; Tevalet; Tri-Minulet; Trigynovin; *Switz.*: Estinette; Femadiol; Gestoden Plus; Gynera; Gyselle; Harmonet; Liosanne; Meliane; Meloden; Milvane; Minesse; Minulet; Mirelle; Myvlar; *Thai.*: Annylyn; Ciclomex; Gynera; Lindynette; Meliane; Minidoz; *Turk.*: Ginera; Minulet; Reginon; *UK*: Femodene; Femodette; Katya; Millinette; Sunya; Triadene; *Ukr.*: Femoden (Фемоден); Lindynette (Линдинет); Logest (Логест); Tristin (Тристин)†; *Venez.*: Avaden; Femiane; Gynera; Harmonet; Minesse; Minulet; Mirelle.

Gestonorone Caproate *(BANM, USAN, rINN)*

Caproato de gestonorona; Caproato de gestronol; Gestonorona, caproato de; Gestonorone, caproate de; Gestonoroni Caproas; Gestronol Hexanoate; Hexanoato de gestonorona; Hexanoato de gestronol; NSC-84054; SH-582; Гестонорона Капроат.

17α-Hydroxy-19-norpregn-4-ene-3,20-dione hexanoate.

$C_{26}H_{38}O_4$=414.6

CAS — 1253-28-7.

ATC — G03DA01; L02AB03.

ATC Vet — QG03DA01; QL02AB03.

UNII — U38E620NS6.

Uses and Administration

Gestonorone caproate is a long-acting potent progestogen structurally related to progesterone (p. 2300.2). It has been given in an oily solution by intramuscular injection in doses of 200 to 400 mg every 5 to 7 days for the adjunctive treatment of endometrial carcinoma (p. 704.3). It has also been used in the management of benign prostatic hyperplasia (p. 2347.1) in doses of 200 mg weekly, increased to 300 to 400 mg weekly if necessary.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3).

Local reactions have occurred at the site of injection. Rarely, coughing, dyspnoea, and circulatory disturbances may develop during or immediately after injection but can be avoided by injecting gestonorone very slowly. In males, spermatogenesis is temporarily inhibited.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Depostat; *Gr.*: Depostat; *Mex.*: Primostat; *Rus.*: Depostat (Депостат).

Gestrinone *(BAN, USAN, rINN)* ⊗

A-46745; Ethylnorgestrienone; Gestrinon; Gestrinona; Gestrinoni; Gestrinonum; R-2323; RU-2323; Гестринон.

13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregna-4,9,11-trien-20-yn-3-one.

$C_{21}H_{24}O_2$=308.4

CAS — 16320-04-0; 40542-65-2.

ATC — G03XA02.

ATC Vet — QG03XA02.

UNII — 1421533RCM.

Uses and Administration

Gestrinone is a synthetic steroidal hormone reported to have antiprogestogenic properties, with some androgenic and anti-oestrogenic activity; it inhibits pituitary gonadotrophin release. It is used in the treatment of endometriosis (p. 2264.1) in oral doses of 2.5 mg twice weekly; the first dose is taken on the first day of the menstrual cycle with the second dose taken three days later; thereafter the doses should be taken on the same two days of each week, usually for a period of 6 months. If a dose is missed it should be given as soon as possible and the original dose sequence maintained thereafter; if 2 or more doses are missed gestrinone should be stopped and restarted on the first day of a new cycle after a negative pregnancy test.

Gestrinone has been studied in the management of cyclical mastalgia (p. 2265.1) and uterine fibroids (p. 2281.2).

References.

1. Thomas EJ, Cooke ID. Impact of gestrinone on the course of asymptomatic endometriosis. *BMJ* 1987; 294: 272–4.
2. Brosens IA, *et al.* The morphologic effect of short-term medical therapy of endometriosis. *Am J Obstet Gynecol* 1987; 157: 1215–21.
3. Coutinho EM, Azadian-Boulanger G. Treatment of endometriosis by vaginal administration of gestrinone. *Fertil Steril* 1988; 49: 418–22.
4. Hornstein MD, *et al.* A randomized double-blind prospective trial of two doses of gestrinone in the treatment of endometriosis. *Fertil Steril* 1990; 53: 237–41.
5. Peters F. Multicentre study of gestrinone in cyclical breast pain. *Lancet* 1992; 339: 205–8.
6. Worthington M, *et al.* A randomized comparative study of the metabolic effects of two regimens of gestrinone in the treatment of endometriosis. *Fertil Steril* 1993; 59: 522–6.
7. Gestrinone Italian Study Group. Gestrinone versus a gonadotropin-releasing hormone agonist for the treatment of pelvic pain associated with endometriosis: a multicenter, randomized, double-blind study. *Fertil Steril* 1996; 66: 911–19.
8. Dawood MY, *et al.* Clinical, endocrine, and metabolic effects of two doses of gestrinone in treatment of pelvic endometriosis. *Am J Obstet Gynecol* 1997; 176: 387–94.
9. La Marca A, *et al.* Gestrinone in the treatment of uterine leiomyomata: effects on uterine blood supply. *Fertil Steril* 2004; 82: 1694–6.

Adverse Effects and Precautions

As for Danazol, p. 2265.3.

Interactions

Antiepileptic drugs and rifampicin may accelerate the metabolism of gestrinone.

Pharmacokinetics

Gestrinone is well absorbed after oral doses with negligible first-pass hepatic metabolism. Peak plasma concentrations occur about 3 hours after a dose. The plasma half-life is about 24 hours. Gestrinone is metabolised in the liver to form conjugated metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nemestran; *Austral.*: Dimetriose; *Braz.*: Dimetrose; *China*: Nemestran (内美通); Yanchang (宫昌); *Ital.*: Dimetrose; *Malaysia*: Dimetriose; *Mex.*: Nemestran; *Neth.*: Nemestran†; *NZ*: Dimetriose; *Port.*: Dimetriose; *Rus.*: Nemestran (Неместран); *S.Afr.*: Tridomose†; *Singapore*: Dimetriose; *Switz.*: Nemestran†; *Thai.*: Dimetriose†; *UK*: Dimetriose†.

Gonadorelin *(BAN, rINN)* ⊗

Follicle Stimulating Hormone-releasing Factor; GnRH; Gonadoliberin; Gonadorellini; Gonadorelina; Gonadoréline; Gonadorelinum; Gonadotrophin-releasing Hormone; Hoe-471; LH/FSH-RF; LH/FSH-RH; LH-RF; LH-RH; Lulliberin; Luteinising Hormone-releasing Factor; Гонадорелин.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosylglycyl-L-leucyl-L-arginyl-L-prolylglycinamide.

$C_{55}H_{75}N_{17}O_{13}$=1182.3

CAS — 33515-09-2.

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

UNII — 9O7312W37G.

Gonadorelin Acetate *(BANM, USAN, rINNM)* ⊗

Abbott-41070; Acetato de gonadorelina; Gonadolrelin-acetát; Gonadorelliniasetaatti; Gonadorelina, acetato de; Gonadorelinacetat; Gonadorelin-acetát; Gonadoréline, acétate de; Gonadorelini acetas; Gonadorelino acetatas; Гонадорелина Ацетат.

$C_{55}H_{75}N_{17}O_{13}xC_2H_4O_2yH_2O$

CAS — 34973-08-5 (anhydrous gonadorelin diacetate); 52699-48-6 (gonadorelin diacetate tetrahydrate).

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

UNII — 2RG1XQ1NYJ (gonadorelin acetate as mixture of monoacetate and diacetate hydrates); L8CRY8PWF2 (gonadorelin diacetate tetrahydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US* for veterinary use only.

USP 36: (Gonadorelin Acetate). A white to slightly yellowish powder. Soluble in water; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature of not more than 8 degrees.

Ph. Eur. 8: (Gonadorelin Acetate). The acetate form of a hypothalamic peptide that stimulates the release of follicle-stimulating hormone and luteinising hormone from the pituitary gland. It is obtained by chemical synthesis. A white or slightly yellowish powder; soluble in water and in 1% v/v glacial acetic acid; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Gonadorelin Hydrochloride

(BANM, USAN, rINNM) ⊗

AY-24031; Gonadorelina, hidrocloruro de; Gonadoréline, Chlorhydrate de; Gonadorelini Hydrochloridum; Hidrocloruro de gonadorelina; Гонадорелина Гидрохлорид.

$C_{55}H_{75}N_{17}O_{13}$,2HCl=1255.2

CAS — 51952-41-1.

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

UNII — 3PFC574ITA.

Pharmacopoeias. In *US*.

USP 36: (Gonadorelin Hydrochloride). A synthetic polypeptide hormone having the property of stimulating the release of the luteinising hormone from the hypothalamus. It is extremely hygroscopic. Protect from exposure to moisture and store in airtight well-sealed containers, in a desiccator.

Uses and Administration

Gonadorelin is a synthetic form of hypothalamic gonadotrophin-releasing hormone. It stimulates the synthesis and release of follicle-stimulating hormone and, in particular, luteinising hormone in the anterior lobe of the pituitary. The secretion of endogenous gonadotrophin-releasing hormone is pulsatile and is controlled by several factors including circulating sex hormones. Gonadotrophic hormones (gonadotrophins), released from the pituitary gland in response to gonadorelin, stimulate secretion of sex hormones from the gonads. A single dose of gonadorelin or one of its analogues has the effect of increasing circulating sex hormones; continued use leads to down-regulation of gonadorelin-receptor synthesis in the pituitary and results in a paradoxical reduction in sex-hormone secretion.

Gonadorelin may be given as the base, acetate, or hydrochloride, and the dose may be expressed in terms of any of these.

Gonadorelin is used in the **diagnosis of hypothalamic-pituitary-gonadal dysfunction** (see p. 2281.1). Assessment is usually based on the response to a dose of gonadorelin of 100 micrograms by intravenous or subcutaneous injection. In females, where possible, it should be given early in the follicular stage of the menstrual cycle. For diagnostic doses used in children, see p. 2281.1.

Gonadorelin is also used in the treatment of **amenorrhoea** (p. 2251.3) and **infertility** (see p. 2281.2) associated with hypogonadotrophic hypogonadism. Weight-related amenorrhoea should have been corrected by diet. Treatment in such conditions is based on an intermittent pulse pump providing 5 to 20 micrograms over one minute every 90 minutes, either subcutaneously or intravenously, for up to 6 months or until conception.

Gonadorelin may be used in the management of *cryptorchidism* (p. 2281.1) and *delayed puberty* (p. 2281.1). Its analogues, such as buserelin, goserelin, leuprorelin,

nafarelin, and triptorelin (which are more potent and have a longer duration of action) can be used in central precocious puberty, endometriosis, uterine fibroids, and malignant neoplasms, especially of the prostate. They may also be used in the management of infertility (see below for further details).

Administration in children. Gonadorelin may be used in the diagnosis of hypothalamic-pituitary-gonadal dysfunction in children (see also below). The *BNFC* includes gonadorelin for children aged from 1 year to 18 years. A single dose of 2.5 micrograms/kg, to a maximum of 100 micrograms, is given subcutaneously or intravenously.

Conditions in which gonadorelin may be used for treatment include cryptorchidism and delayed puberty. Gonadorelin analogues are used in precocious puberty (see below).

Benign prostatic hyperplasia. The gonadorelin analogues have been tried in the management of benign prostatic hyperplasia (p. 2347.1) but are considered unsatisfactory for indefinite use. See also under Leuprorelin, p. 2286.1, and Nafarelin Acetate, p. 2292.2.

Cryptorchidism. Although surgery remains the treatment with the best success rate, primary hormonal therapy with gonadorelin may be used for cryptorchidism (p. 2252.1). Systematic reviews[1,2] suggest a success rate of about 20% overall, although this may be reduced when care is taken to exclude retractile testes. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, which may be a predictor of future fertility.[3]

Gonadorelin is usually given intranasally, in a dose of 1.2 mg daily, in 3 divided doses, for 4 weeks.[3]

1. Pyörälä S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; 80: 2795–9.
2. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; 20: 357–9.
3. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (update March 2009). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Paediatric_Urology.pdf (accessed 28/10/09)

Delayed puberty. Gonadorelin may be used in the management of delayed puberty (p. 2252.1) that is secondary to hypogonadotrophic hypogonadism. It is given to boys to stimulate the release of endogenous gonadotrophins that are needed for testicular development.[1] In order to mimic the pulsatile release of endogenous gonadotrophin-releasing hormone, gonadorelin acetate or hydrochloride is given subcutaneously or intravenously, in pulses of about 5 to 20 micrograms at intervals of 90 to 120 minutes. Treatment may be given for 30 to 50 weeks.

1. Delemarre EM, *et al.* Inducing puberty. *Eur J Endocrinol* 2008; 159 (suppl): S9–S15.

Diagnosis of hypothalamic and pituitary dysfunction. Gonadorelin may be used in the diagnosis of hypothalamic-pituitary-gonadal dysfunction such as in hypogonadism, delayed puberty, and precocious puberty.[1,2] Gonadorelin analogues, such as triptorelin (p. 2311.1), have also been used in the diagnosis of delayed puberty.

1. Ecker KL, *et al.* A single-sample, subcutaneous gonadotropin-releasing hormone test for central precocious puberty. *Pediatrics* 1996; 97: 517–19.
2. De Martino MU, *et al.* Dynamic testing in the evaluation of male gonadal function. *J Endocrinol Invest* 2003; 26 (suppl): 107–13.

Disturbed behaviour. Gonadorelin analogues such as leuprorelin (p. 2286.1) or triptorelin (p. 2311.2) may be tried in men with paraphilias.

Reviews.

1. Briken P, *et al.* Pharmacotherapy of paraphilias with long-acting agonists of luteinizing hormone-releasing hormone: a systematic review. *J Clin Psychiatry* 2003; 64: 890–7.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p. 2264.1), but the need for long-term therapy to prevent recurrence limits their value, because of the risk of osteoporosis. 'Add-back' therapy (hormone replacement) may be given in an attempt to reduce bone mineral density loss and vasomotor symptoms.

Some references to gonadorelin analogues in endometriosis are listed below. For further references, see Buserelin, p. 2256.3, Goserelin, p. 2283.1, Leuprorelin, p. 2286.1, Nafarelin Acetate, p. 2292.2, and Triptorelin, p. 2311.2.

1. Gargiulo AR, Hornstein MD. The role of GnRH agonists plus add-back therapy in the treatment of endometriosis. *Semin Reprod Endocrinol* 1997; 15: 273–84.
2. Hemmings R. Combined treatment of endometriosis: GnRH agonists and laparoscopic surgery. *J Reprod Med* 1998; 43 (suppl 3): 316–20.
3. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; 105: 475–85.
4. Surrey ES. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? *Fertil Steril* 1999; 71: 420–4.
5. Olive DL. Gonadotropin-releasing hormone agonists for endometriosis. *N Engl J Med* 2008; 359: 1136–42.

Fibroids. Uterine fibroids (leiomyomas) are benign tumours of uterine smooth muscle.[1-3] They are found in about 25% of women, most of whom are aged in their 30s or 40s when the condition becomes symptomatic. Fibroids may give rise to menstrual problems, particularly menorrhagia, pelvic discomfort, infertility, and miscarriage. Although small fibroids may not require treatment, the management of symptomatic fibroids has traditionally been surgical. However, because fibroids are oestrogen responsive, gonadorelin analogues have also been tried as medical treatment for their ability to induce a hypogonadotrophic hypogonadal state. These drugs produce a significant reduction in uterine and fibroid volume, and amenorrhoea, but when treatment stops uterine and fibroid volume tend to return to pretreatment values. The hypoestrogenism produced during treatment also causes menopausal symptoms such as hot flushes and vaginal dryness, and bone loss may occur. Giving oestrogens or progestogens, once the uterine fibroid size has significantly reduced, has been tried as 'add-back' therapy to counteract these adverse effects.[4,5] Tibolone has also been reported to reduce bone loss and vasomotor symptoms.[2,3] Subcutaneous injection of long-acting depot preparations of gonadorelin or its analogues appears to be the preferred method and is considered a valuable pre-operative adjunct to surgery, simplifying the procedure by reducing uterine and fibroid volume and intra-operative blood loss, as well as correcting pre-operative iron-deficiency anaemia.[6,7] However, not all centres favour general pre-operative use,[3] and concern has been expressed that the use of gonadorelin analogues for treating fibroids may complicate the differentiation of benign and malignant growths,[8] or cause smaller fibroids to be missed at excision.[3]

For further references to use of gonadorelin analogues in the treatment of fibroids, see Buserelin, p. 2256.3, Goserelin, p. 2283.1, Leuprorelin, p. 2286.1, Nafarelin Acetate, p. 2292.3, and Triptorelin, p. 2311.2.

Ulipristal acetate, a progesterone receptor modulator, may be used pre-operatively to control excessive bleeding and reduce fibroid size.[9] It may control bleeding more quickly than leuprorelin, but be less effective in reducing uterine volume.[10] Other drugs that are under investigation for fibroids include gonadorelin antagonists such as cetrorelix and ganirelix, and mifepristone. Danazol and gestrinone have also been tried in a small number of patients.[2,3]

1. Stewart EA. Uterine fibroids. *Lancet* 2001; 357: 293–8.
2. De Leo V, *et al.* A benefit-risk assessment of medical treatment for uterine leiomyomas. *Drug Safety* 2002; 25: 759–79.
3. Sankaran S, Manyonda IT. Medical management of fibroids. *Best Pract Res Clin Obstet Gynaecol* 2008; 22: 655–76.
4. Friedman AJ, *et al.* Efficacy and safety considerations in women with uterine leiomyomas treated with gonadotropin-releasing hormone agonists: the estrogen threshold hypothesis. *Am J Obstet Gynecol* 1990; 163: 1114–19.
5. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; 105: 475–85.
6. Lethaby A, *et al.* Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 15/09/05).
7. Agence Française de Sécurité Sanitaire des Produits de Santé. Les traitements médicamenteux du fibrome utérin - octobre 2004. Available at: http://www.afssaps.sante.fr/content/download/3971/39226/version/4/file/fibrorec.pdf (accessed 19/07/10)
8. Mesia AF, *et al.* Aborted leiomyosarcoma after treatment with leuprolide acetate. *Obstet Gynecol* 1998; 92: 664–6.
9. Donnez J, *et al.* PEARL I Study Group. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med* 2012; 366: 409–20.
10. Donnez J, *et al.* PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med* 2012; 366: 421–32.

Growth retardation. The use of a gonadorelin analogue to delay precocious puberty may improve the final height of children with the disorder. However, the use of a gonadorelin analogue with growth hormone in short but otherwise normal children is controversial—see under Triptorelin, p. 2311.2.

Hirsutism. For reference to the use of gonadorelin analogues such as leuprorelin in the treatment of hirsutism, see p. 2286.1.

Infertility. Gonadorelin and its analogues are used in the management of infertility related to hypogonadotrophic hypogonadism in both women and men (p. 2253.1). Some further references are given below. See also under Buserelin, p. 2256.3, Leuprorelin, p. 2286.2, and Nafarelin Acetate, p. 2292.3.

For mention of the use of gonadorelin and its analogues in the management of infertility in polycystic ovary syndrome, see below.

1. Lingle L, Hart LL. Gonadotropin-releasing hormone in infertility. *DICP Ann Pharmacother* 1989; 23: 246–8.
2. Thomas AK, *et al.* Induction of ovulation with subcutaneous pulsatile gonadotropin-releasing hormone: correlation with body weight and other parameters. *Fertil Steril* 1989; 51: 786–90.
3. Homburg R, *et al.* One hundred pregnancies after treatment with pulsatile luteinising hormone releasing hormone to induce ovulation. *BMJ* 1989; 298: 809–12.
4. Kovacs GT, *et al.* Induction of ovulation with gonadotrophin-releasing hormone—life-table analysis of 50 courses of treatment. *Med J Aust* 1989; 151: 21–6.
5. Santoro N. Efficacy and safety of intravenous pulsatile gonadotropin-releasing hormone: Lutrepulse for injection. *Am J Obstet Gynecol* 1990; 163: 1759–64.
6. Nachtigall LB, *et al.* Adult-onset idiopathic hypogonadotropic hypogonadism—a treatable form of male infertility. *N Engl J Med* 1997; 336: 410–15.

Malignant neoplasms. Gonadorelin analogues are used in the treatment of prostatic cancer (p. 712.3) where they provide an alternative to orchidectomy in the management of advanced disease. They may also be used for ovarian ablation in premenopausal women with breast cancer (p. 702.1). Gonadorelin analogues have been tried in neoplasms of the endometrium and ovary, but their use is much less well established.

Analogues used include buserelin (p. 2256.3), goserelin (p. 2283.1), leuprorelin (p. 2286.2), and triptorelin (p. 2311.2).

Mastalgia. Gonadorelin analogues such as goserelin may be effective in severe refractory mastalgia (p. 2265.1).

Polycystic ovary syndrome. Gonadorelin and its analogues have been used in the management of infertility associated with polycystic ovary syndrome (see Infertility, p. 2253.1), even though some product information contra-indicates their use in this syndrome.

Pulsatile gonadorelin has been tried for ovulation induction but rates of ovulation and pregnancy are poor when it is used alone in women with polycystic ovary syndrome. Pretreatment with a gonadorelin analogue for pituitary desensitisation before starting pulsatile gonadorelin has shown some benefit in patients with polycystic ovary syndrome who have high levels of luteinising hormone.[1] However, there are only limited clinical data from small short-term studies and case series on the use of pulsatile gonadorelin in these women.[2]

Gonadorelin analogues may be used for pituitary desensitisation before the use of gonadotrophins for ovulation induction, and there is a suggestion that this strategy may improve pregnancy rates compared with gonadotrophins alone in women with polycystic ovary syndrome.[3] Gonadorelin analogues are used also in ovarian stimulation protocols for assisted reproduction techniques.[1]

Women with polycystic ovary syndrome are at increased risk of ovarian hyperstimulation syndrome and must be carefully monitored throughout the use of ovulation induction regimens.[1]

1. Buckett WM, Tan SL. Use of luteinizing hormone releasing hormone agonists in polycystic ovary syndrome. *Baillieres Clin Obstet Gynaecol* 1998; 12: 593–606.
2. Bayram N, *et al.* Pulsatile gonadotrophin releasing hormone for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 15/09/05).
3. Nugent D, *et al.* Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 15/09/05).

Porphyria. For mention of the use of gonadorelin analogues to suppress cyclic premenstrual exacerbations of acute porphyria, see Buserelin, p. 2257.1, Nafarelin Acetate, p. 2292.3, and Triptorelin, p. 2311.3.

Precocious puberty. Gonadorelin analogues are the treatment of choice in central precocious puberty (p. 2254.1).[1] Analogues used include buserelin (p. 2257.1), goserelin (p. 2283.2), histrelin (p. 2284.1), leuprorelin (p. 2286.2), nafarelin (p. 2292.3), and triptorelin (p. 2311.3).

1. Carel J-C, *et al.* ESPE-LWPES GnRH Analogs Consensus Conference Group. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Abstract: *Pediatrics* 2009; 123: 1242. Full version: http://pediatrics.aappublications.org/cgi/reprint/123/4/e752 (accessed 28/10/09)

Premenstrual syndrome. In women in whom other drug treatments for premenstrual syndrome (p. 2272.3) are ineffective, use of a gonadorelin analogue, usually with HRT as 'add-back' therapy to prevent menopausal symptoms, may be considered.[1] Short-term therapy (3 months) has been used to confirm the diagnosis of premenstrual syndrome, or to predict the response to bilateral oophorectomy when this is being considered. Some references to the use of gonadorelin analogues in premenstrual syndrome are given below.[2-7]

1. Wyatt KM, *et al.* The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis. *Br J Obstet Gynaecol* 2004; 111: 585–93.
2. Hussain ST, *et al.* Buserelin in premenstrual syndrome. *Gynecol Endocrinol* 1992; 6: 57–64.
3. Mezrow G, *et al.* Depot leuprolide acetate with estrogen and progestin add-back for long-term treatment of premenstrual syndrome. *Fertil Steril* 1994; 62: 932–7.

4. Brown CS, *et al.* Efficacy of depot leuprolide in premenstrual syndrome: effect of symptom severity and type in a controlled trial. *Obstet Gynecol* 1994; **84:** 779–86.
5. West CP, Hillier H. Ovarian suppression with the gonadotrophin-releasing hormone agonist goserelin (Zoladex) in management of the premenstrual tension syndrome. *Hum Reprod* 1994; **9:** 1058–63.
6. Leather AT, *et al.* The treatment of severe premenstrual syndrome with goserelin with and without 'add-back' estrogen therapy: a placebo-controlled study. *Gynecol Endocrinol* 1999; **13:** 48–55.
7. Di Carlo C, *et al.* Use of leuprolide acetate plus tibolone in the treatment of severe premenstrual syndrome. *Fertil Steril* 2001; **75:** 380–4.

Adverse Effects

Gonadorelin and its analogues are generally well tolerated but may cause gastrointestinal adverse effects, usually nausea and abdominal pain or discomfort. There may be headache or lightheadedness, and an increase in menstrual bleeding. Continued therapy with gonadorelin analogues results in paradoxical suppression of the pituitary gonadal axis; in premenopausal women this may produce menopausal symptoms, including vaginal dryness, hot flushes, and loss of libido. If sufficiently prolonged the suppression of circulating oestrogens may lead to osteoporosis. In men, hot flushes and sexual dysfunction can occur, and breast swelling and tenderness have been reported infrequently with gonadorelin analogues. Long-term treatment can also cause a loss of bone mineral density in men. Other adverse effects reportedly associated with gonadorelin analogue therapy, and presumably related to changes in the hormonal milieu, include mood changes, nervousness, palpitations, acne and dry skin, changes in scalp and body hair, alterations in liver function tests and blood lipids, and decreased glucose tolerance. Arthralgia and paraesthesias have been reported. Ovarian hyperstimulation (as seen with chorionic gonadotrophin, p. 2258.3), although rare, has occurred in women given gonadorelin.

Reactions or pain may occur at the site of injection with rash (local or generalised), thrombophlebitis, swelling, or pruritus. Hypersensitivity reactions, including bronchospasm and anaphylaxis, have been reported. Convulsions have occurred in patients given gonadorelin analogues.

Other effects may be a consequence of the particular use of gonadorelin or its analogues. Tumour flare, due to an initial surge in testosterone concentrations, has been reported in the initial stages of treatment for cancer of the prostate and prophylactic anti-androgen therapy may be added. Flare may manifest as an increase in bone pain; occasionally there has been spinal cord compression, or a worsening of urinary-tract symptoms with haematuria and urinary obstruction. Acute degeneration of submucous fibroids with severe bleeding has been reported following use of leuprorelin. An initial increase in signs and symptoms has also been reported in women with breast cancer receiving gonadorelin analogues; hypercalcaemia has occurred in those with metastatic disease. In girls being treated for precocious puberty, vaginal bleeding may occur in the first month of treatment because of initial ovarian stimulation followed by treatment-induced oestrogen withdrawal.

Effects on the cardiovascular system. Gonadorelin analogues are widely used as a component of androgen deprivation therapy in the treatment of prostate cancer. However, the hypogonadism associated with this therapy may contribute to the development of metabolic complications such as insulin resistance, hyperglycaemia, dyslipidaemia, and the metabolic syndrome. There is some evidence that long-term use of androgen deprivation therapy may increase the risk of diabetes, atherosclerosis, and cardiovascular disease.

References.
1. Keating NL, *et al.* Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006; **24:** 4448–56.
2. Saigal CS, *et al.* Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer* 2007; **110:** 1493–1500.
3. Tsai HK, *et al.* Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst* 2007; **99:** 1516–24.
4. Shahani S, *et al.* Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. *J Clin Endocrinol Metab* 2008; **93:** 2042–9.

Hypersensitivity. Acquired hypersensitivity led to an anaphylactic reaction after an intravenous dose of gonadorelin in a man who had been receiving pulsatile subcutaneous gonadorelin therapy for 10 weeks.[1]

1. Potashnik G, *et al.* Anaphylactic reaction to gonadotropin-releasing hormone. *N Engl J Med* 1993; **328:** 815.

Osteoporosis. Long-term use of a gonadorelin analogue results in oestrogen deficiency-associated osteoporosis and various drugs have been investigated for their ability to reduce this effect. Parathyroid hormone has been reported to prevent bone loss in small studies of young women receiving nafarelin.[1,2] 'Add-back' therapy with tibolone[3,4] or oestrogen plus progestogen[5,6] has also had beneficial effects on bone mineral density in women receiving gonadorelin analogues. However, studies have used various combination regimens and it is not possible to determine which is most effective.[6,7] There is less information available about the management of osteoporosis in men receiving gonadorelin analogues as androgen deprivation therapy, but measures have included supplemental calcium and vitamin D, and the use of bisphosphonates.[8] Raloxifene is also under investigation in both women[9] and men.[10]

1. Finkelstein JS, *et al.* Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. *N Engl J Med* 1994; **331:** 1618–23.
2. Finkelstein JS, *et al.* Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA* 1998; **280:** 1067–73.
3. Lindsay PC, *et al.* The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). *Fertil Steril* 1996; **65:** 342–8.
4. Palomba S, *et al.* A clinical trial of the effects of tibolone administered with gonadorelin-releasing hormone analogues for the treatment of uterine leiomyomata. *Fertil Steril* 1998; **70:** 111–18.
5. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.
6. Sagsveen M, *et al.* Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 15/09/05).
7. Surrey ES, the Add-back Consensus Working Group. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? *Fertil Steril* 1999; **71:** 420–4.
8. Smith MR. Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. *Cancer* 2003; **97** (suppl): 789–95.
9. Palomba S, *et al.* Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. *J Clin Endocrinol Metab* 2002; **87:** 4476–81.
10. Smith MR, *et al.* Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3841–6.

Pituitary apoplexy. Pituitary apoplexy has been reported after endocrine stimulation testing using gonadorelin. A review[1] of 14 cases found that 2 patients had received gonadorelin alone but most had also received protirelin (thyrotropin-releasing hormone). The onset of initial symptoms was within 2 hours and pituitary tumour haemorrhage was much more common than infarction alone.

1. Matsuura I, *et al.* Infarction followed by hemorrhage in pituitary adenoma due to endocrine stimulation test. *Endocr J* 2001; **48:** 493–8.

Precautions

Gonadorelin or its analogues should not generally be used in patients with pituitary adenoma as haemorrhagic infarction (pituitary apoplexy) has sometimes occurred. It has also been recommended that patients with weight-related amenorrhoea should not receive these drugs until their weight is corrected. Although at least one manufacturer recommends that gonadorelin should not be used in women with polycystic ovary disease or with endometriotic cysts, gonadorelin and its analogues have been used for ovulation induction in polycystic disease and produced improvement in uterine fibroids; gonadorelin analogues have also been used with benefit in endometriosis. Gonadorelin analogues may increase cervical resistance, making it difficult to dilate the cervix for intra-uterine surgical procedures. Gonadorelin or its analogues should be stopped if the patient becomes pregnant. Contraceptive measures should be taken to protect against unwanted ovulation. Men at risk from tumour flare should be carefully monitored in the first month of therapy. Patients with diabetes should be monitored for effects on glucose control.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gonadorelin as possibly porphyrinogenic: it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1] NAPOS classifies several gonadorelin analogues as porphyrinogenic: buserelin (p. 2257.1), goserelin (p. 2283.2), leuprorelin (p. 2287.1), and triptorelin (p. 2311.3); or as possibly porphyrinogenic: nafarelin (p. 2292.3).

For reference to the use of gonadorelin analogues to prevent premenstrual exacerbations of acute porphyria, see p. 2281.3.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Drugs affecting pituitary secretion of gonadotrophins may alter the response to gonadorelin or its analogues; other hormonal therapy and corticosteroids can affect the response. Spironolactone and levodopa can stimulate gonadotrophins while phenothiazines, dopamine antagonists, digoxin, and sex hormones can inhibit gonadotrophin secretion.

Pharmacokinetics

Gonadorelin is poorly absorbed from the gastrointestinal tract. It has a terminal plasma half-life of only 10 to 40 minutes after intravenous injection. It is hydrolysed in the plasma and excreted in the urine as inactive metabolites.

Gonadorelin analogues are absorbed after oral, intramuscular, intranasal, or rectal doses and have a longer half-life.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Luteoliberina; ***Austria:*** Kryptocur; Lutrelef; Relefact LH-RH†; ***Belg.***: HRF; ***Canad.***: Lutrepulse; Relisorm; ***Fr.***: Lutrelef; Stimu-LH†; ***Ger.***: Kryptocur; Lutrelef; Relefact LH-RH; ***Gr.***: Cryptocur; Relefact LH-RH; Relisorm; ***Irl.***: HRF; ***Ital.***: Kryptocur; Lutrelef; ***Neth.***: HRF†; Lutrelef; Relefact LH-RH; ***S.Afr.***: HRF†; ***Swed.***: Lutrelef†; ***Switz.***: Kryptocur†; Lutrelef; ***UK***: HRF; ***USA***: Factrel†.

Pharmacopoeial Preparations
USP 36: Gonadorelin for Injection.

Goserelin *(BAN, USAN, rINN)* ⊗

Gosereliini; Goserelina; Goserelinas; Goséréline; Goserelinum; Goszerelin; ICI-118630; Гозерелин.

3-[5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-(3-*O*-*tert*-butyl)-D-seryl-L-leucyl-L-arginyl-L-prolyl]carbazamide.

$C_{59}H_{84}N_{18}O_{14}$=1269.4

CAS — 65807-02-5.
ATC — L02AE03.
ATC Vet — QL02AE03.
UNII — 0F65R8P09N.

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

Ph. Eur. 8: (Goserelin). A nonapeptide analogue of the hypothalamic decapeptide, gonadorelin. It is obtained by chemical synthesis and is available as an acetate. A white or almost white powder. Soluble in water; freely soluble in glacial acetic acid. It dissolves in dilute solutions of mineral acids and alkali hydroxides. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Goserelin Acetate *(BANM, rINNM)* ⊗

Acetato de goserelina; Goserelina, acetato de; Goséréline, Acétate de; Goserelini Acetas; D-Ser(Bu^t)^6 Azgly^{10}-LHRH Acetate; Гозерелина Ацетат.

$C_{59}H_{84}N_{18}O_{14}.C_2H_4O_2$=1329.5

CAS — 145781-92-6.
ATC — L02AE03.
ATC Vet — QL02AE03.
UNII — 6YUU2PV0U8.

Pharmacopoeias. In *US.*

USP 36: (Goserelin Acetate). Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Goserelin is an analogue of gonadorelin (p. 2280.3) with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, in breast cancer in pre-and perimenopausal women, and in the management of endometriosis. Limited courses of treatment are given for endometrial thinning before surgery for dysfunctional uterine bleeding, and with iron supplementation to improve anaemia before surgery in women being treated for fibroids. It is also used as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility. Goserelin is usually given as the acetate but doses are expressed in terms of the base; 10.5 mg of goserelin acetate is equivalent to about 10 mg of goserelin.

Goserelin acetate is generally given in biodegradable implants, which are injected subcutaneously into the anterior abdominal wall. The continuous release of drug gradually suppresses serum concentrations of oestradiol and testosterone over about 3 weeks after the first injection, and low hormone concentrations are maintained with repeated doses. One such preparation containing the equivalent of 3.6 mg of goserelin is given once every 28 days in the treatment of **prostate** and **breast cancers**. Preparations containing the equivalent of 10.8 mg of goserelin, given every 12 weeks, are also available for the treatment of prostate cancer. In the treatment of prostate cancer an anti-androgen such as cyproterone acetate may be given for several days before starting goserelin therapy and continued for at least 3 weeks, to avoid the risk of a disease flare.

Preparations containing the equivalent of 3.6 mg of goserelin given once every 28 days are also used to treat **endometriosis** for up to 6 months. For **endometrial thinning** before surgery in dysfunctional uterine bleeding,

a single dose is given 4 weeks before surgery. Some women may require a second dose to provide 8 weeks of treatment—for example, those with a large uterus or to allow flexible timing of surgery. In women with anaemia as a result of uterine fibroids, goserelin 3.6 mg is given with iron supplementation for up to 3 months before surgery.

In infertility, regimens for oocyte collection for IVF use gonadorelin analogues for pituitary desensitisation before ovulation induction with gonadotrophins. The equivalent of 3.6 mg of goserelin is given as a subcutaneous implant and serum-oestradiol concentrations monitored until they decline to levels similar to those in the early follicular phase, a process which usually takes 7 to 21 days. Once downregulation occurs gonadotrophin (follicle stimulating) therapy is begun until an appropriate stage of follicular development, when it is withdrawn and chorionic gonadotrophin is given to induce ovulation.

Goserelin has also been given in other sex-hormone-related conditions. For the use of goserelin in children, see below.

Reviews of goserelin.

1. Chrisp P, Goa KL. Goserelin: a review of its pharmacodynamic and pharmacokinetic properties, and clinical use in sex hormone-related conditions. *Drugs* 1991; 41: 254–88.
2. Perry CM, Brogden RN. Goserelin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in benign gynaecological disorders. *Drugs* 1996; 51: 319–46.

Administration in children. Goserelin may be used in the management of central precocious puberty—see below.

Endometriosis. Gonadorelin analogues such as goserelin are effective in the management of endometriosis (p. 2264.1), but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis. Hormone replacement (add-back therapy) may also be given in an attempt to reduce bone mineral density loss and vasomotor symptoms in women receiving goserelin.

References.

1. Shaw RW, *et al.* An open randomized comparative study of the effect of goserelin depot and danazol in the treatment of endometriosis. *Fertil Steril* 1992; 58: 265–72.
2. Schlaff WD. Extending the treatment boundaries: Zoladex and add-back. *Int J Gynaecol Obstet* 1999; 64 (suppl 1): S25–S31.
3. Pranke HR, *et al.* Gonadotropin-releasing hormone agonist plus "add-back" hormone replacement therapy for treatment of endometriosis: a prospective, randomized, placebo-controlled, double-blind trial. *Fertil Steril* 2000; 74: 534–9.
4. Pierce SJ, *et al.* Long-term use of gonadotropin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. *Fertil Steril* 2000; 74: 964–8.

Fibroids. Gonadorelin analogues such as goserelin have been tried as an adjunct or an alternative to surgery in the treatment of uterine fibroids (p. 2281.2) although there has been some concern that this might complicate the diagnosis of malignancy. Some further references are listed below.

1. Lumsden MA, *et al.* Treatment with the gonadotrophin releasing hormone-agonist goserelin before hysterectomy for uterine fibroids. *Br J Obstet Gynaecol* 1994; 101: 438–42.
2. Benagiano G, *et al.* Zoladex (goserelin acetate) and the anemic patient: results of a multicenter fibroid study. *Fertil Steril* 1996; 66: 223–9.
3. Parazzini F, *et al.* Goserelin acetate to avoid hysterectomy in premenopausal women with fibroids requiring surgery. *Eur J Obstet Gynecol Reprod Biol* 1999; 87: 31–3.
4. Bozzini N, *et al.* Comparative study of different dosages of goserelin in size reduction of myomatous uteri. *J Am Assoc Gynecol Laparosc* 2004; 11: 462–3.
5. Muneyyirci-Delale O, *et al.* Goserelin acetate 10.8 mg plus iron versus iron monotherapy prior to surgery in premenopausal women with iron-deficiency anemia due to uterine leiomyomas: results from a phase III, randomized, multicenter, double-blind, controlled trial. *Clin Ther* 2007; 29: 1682–91.
6. Lim SS, *et al.* Goserelin versus leuprolide before hysterectomy for uterine fibroids. *Int J Gynaecol Obstet* 2008; 101: 178–83.

Malignant neoplasms. Goserelin is effective in the treatment of prostate cancer (p. 712.3). It has produced a response similar to that of orchidectomy (surgical removal of the testes) in patients with metastatic prostate cancer.[1] Goserelin has been combined with an anti-androgen such as flutamide to provide maximum androgen blockade, but this appears to produce modest additional benefits at most. There is some evidence[2,3] that adjuvant therapy with goserelin may improve survival in patients with localised or locally advanced prostate cancer when combined with radiotherapy or radical prostatectomy, and adjuvant use of goserelin appears to be more beneficial than neoadjuvant use.[2]

Goserelin may also be used as hormonal therapy in premenopausal women with advanced breast cancer (p. 702.1); it seems to be as effective as oophorectomy,[4] and use with tamoxifen is more effective than goserelin alone.[5] It is also used as an alternative or addition to adjuvant chemotherapy in pre- or peri-menopausal women with oestrogen-receptor positive early breast cancer,[6-12] and has been investigated for its potential to preserve ovarian function in this group.[12]

1. Seidenfeld J, *et al.* Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; 132: 566–77. Correction. *ibid.* 2005; 143: 764–5.
2. Akaza H. Adjuvant goserelin improves clinical disease-free survival and reduces disease-related mortality in patients with locally advanced or localized prostate cancer. *BJU Int* 2004; 93: 42–6.
3. Roach M, Izaguirre A. Goserelin acetate in combination with radiotherapy for prostate cancer. *Expert Opin Pharmacother* 2007; 8: 257–64.
4. Taylor CW, *et al.* Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. *J Clin Oncol* 1998; 16: 994–9.
5. Klijn JGM, *et al.* Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; 19: 343–53.
6. Jakesz R, *et al.* Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002; 20: 4621–7.
7. Jonat W, *et al.* Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association Study. *J Clin Oncol* 2002; 20: 4628–35.
8. International Breast Cancer Study Group (IBCSG). Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003; 95: 1833–46.
9. Cheer SM, *et al.* Goserelin: a review of its use in the treatment of early breast cancer in premenopausal and perimenopausal women. *Drugs* 2005; 65: 2639–55.
10. Baum M, *et al.* ZIPP International Collaborators' Group. Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. *Eur J Cancer* 2006; 42: 895–904.
11. Hackshaw A, *et al.* Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer. *J Natl Cancer Inst* 2009; 101: 341–9.
12. Sverrisdottir A, *et al.* Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: results from a randomized trial. *Breast Cancer Res Treat* 2009; 117: 561–7.

Mastalgia. For reference to the use of goserelin in mastalgia, see under Danazol, p. 2265.1.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p. 2254.1). Although not licensed for use in children in the UK, the *BNFC* includes doses of goserelin for central precocious puberty. Implants are given by subcutaneous injection into the anterior abdominal wall; preparations that contain a dose of 3.6 mg are given once every 28 days, another containing 10.8 mg is given once every 12 weeks. Injections may be needed more frequently in some patients.

References to the use of goserelin.

1. Trueman JA, *et al.* Suppression of puberty with long-acting goserelin (Zoladex-LA): effect on gonadotrophin response to GnRH in the first treatment cycle. *Clin Endocrinol (Oxf)* 2002; 57: 223–30.
2. Paterson WF, *et al.* Auxological outcome and time to menarche following long-acting goserelin therapy in girls with central precocious or early puberty. *Clin Endocrinol (Oxf)* 2004; 61: 626–34.
3. Isaac H, *et al.* Efficacy of a monthly compared to 3-monthly depot GnRH analogue (goserelin) in the treatment of children with central precocious puberty. *Horm Res* 2007; 68: 157–63.
4. Mouat F, *et al.* Initial growth deceleration during GnRH analogue therapy for precocious puberty. *Clin Endocrinol (Oxf)* 2009; 70: 751–6.

Premenstrual syndrome. For reference to the use of goserelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug treatment, see under Gonadorelin, p. 2281.3.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1. Some women may have vaginal bleeding during initial therapy, which normally resolves spontaneously.

Pituitary apoplexy. Pituitary apoplexy (a clinical syndrome caused by haemorrhage and infarction of a pituitary adenoma) occurred in a few elderly patients with a symptomless pituitary adenoma who were given goserelin for advanced prostate cancer.[1,2] Symptoms included headache, vomiting, visual disturbances, gradual impairment of consciousness, intermittent fever, and progressive hyponatraemia. Symptoms were treated with corticosteroid replacement therapy.

1. Ando S, *et al.* Pituitary apoplexy after goserelin. *Lancet* 1995; 345: 458.
2. Baton HJ, *et al.* Rapid onset of pituitary apoplexy after goserelin implant for prostate cancer: need for heightened awareness. *Intern Med J* 2001; 31: 313–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies goserelin 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 06/10/11)

Pharmacokinetics

Goserelin is almost completely absorbed after subcutaneous injection, and has a serum elimination half-life of 2 to 4 hours, which may be increased in renal impairment. More than 90% of a dose is excreted in urine, as unchanged drug and metabolites.

Reviews.

1. Cockshott ID. Clinical pharmacokinetics of goserelin. *Clin Pharmacokinet* 2000; 39: 27–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Goselin; Larmadex; Zoladex; *Austral.*: Zoladex; *Austria*: Zoladex; *Belg.*: Zoladex; *Braz.*: Zoladex; *Canad.*: Zoladex; *Chile*: Vacromil†; Vicromil†; Zoladex; *China*: Zoladex (诺雷得); *Cz.*: Zoladex; *Denm.*: Zoladex; *Fin.*: Zoladex; *Fr.*: Zoladex; *Ger.*: Zoladex; *Gr.*: Zoladex; *Hong Kong*: Zoladex; *Hung.*: Zoladex; *Indon.*: Zoladex; *Irl.*: Zoladex; *Israel*: Zoladex; *Ital.*: Zoladex; *Malaysia*: Zoladex; *Mex.*: Zoladex; *Neth.*: Zoladex; *Norw.*: Zoladex; *NZ*: Zoladex; *Philipp.*: Zoladex; *Pol.*: Zoladex; *Port.*: Zoladex; *Russ.*: Zoladex (Золадекс); *S.Afr.*: Zoladex; *Singapore*: Zoladex; *Spain*: Zoladex; *Swed.*: Zoladex; *Switz.*: Zoladex; *Thai.*: Zoladex; *Turk.*: Zoladex; *UK*: Novgos†; Zoladex; *Ukr.*: Zoladex (Золадекс); *USA*: Zoladex; *Venez.*: Zoladex.

Multi-ingredient Preparations. *Arg.*: Zolapack; *Austral.*: ZolaCos CP; *NZ*: ZolaCos CP.

Pharmacopoeial Preparations
BP 2014: Goserelin Implants.

Hexestrol *(rINN)*

Dihydrodiethylstilboestrol; Dihydrostilboestrol; Hexanoestrol; Hexestrolum; Hexoestrol; NSC-9894; Synestrol; Synoestrol; Fexocipon.

4,4'-(1,2-Diethylethylene)diphenol.

$C_{18}H_{22}O_2$ = 270.4.

CAS — 5635-50-7 (hexestrol); 84-16-2 (meso-hexestrol).

UNII — 108795R7O.

Profile

Hexestrol is a synthetic nonsteroidal oestrogen that is used for oestrogen replacement therapy and in the treatment of malignant neoplasms and gynaecological disorders.

Histrelin *(USAN, rINN)* ⊗

Histrelina; Histréline; Histrelinum; ORF-17070; RWJ-17070; Гистрелин.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*N*^{5}-benzyl-D-histidyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

$C_{66}H_{86}N_{18}O_{12}$ = 1323.5

CAS — 76712-82-8.

ATC — L02AE05.

ATC Vet — QL02AE05.

UNII — H50H353W74.

Histrelin Acetate *(rINNM)* ⊗

Acetato de histrelina; Histrelina, acetato de; Histréline, Acétate d'; Histrelini Acetas; Гистрелина Ацетат.

$C_{66}H_{86}N_{18}O_{12}.C_2H_4O_2.xH_2O$

CAS — 220810-26-4.

ATC — L02AE05.

ATC Vet — QL02AE05.

UNII — QMG7HLD1ZE.

Uses and Administration

Histrelin is an analogue of gonadorelin (p. 2280.3) with similar properties. A subcutaneous implant containing histrelin acetate 50 mg, and designed to release about 50 micrograms daily for 12 months, is used in the palliative treatment of advanced prostate cancer (p. 712.3).

Histrelin is used in the treatment of precocious puberty in children (see p. 2284.1). It has also been investigated in disorders related to the menstrual cycle, and in the treatment of acute porphyrias.

References.

1. Anderson KE, *et al.* A gonadotropin releasing hormone analogue prevents cyclical attacks of porphyria. *Arch Intern Med* 1990; 150: 1469–74.
2. Moriola JF, *et al.* Successful treatment of severe premenstrual syndrome by combined use of gonadotropin-releasing hormone agonist and estrogen/progestin. *J Clin Endocrinol Metab* 1991; 72: 252A–F.
3. Cheung AP, Chang RJ. Pituitary responsiveness to gonadotrophin-releasing hormone agonist stimulation: a dose-response comparison of luteinizing hormone/follicle-stimulating hormone secretion in women with polycystic ovary syndrome and normal women. *Hum Reprod* 1995; 10: 1054–9.
4. Chertin B, *et al.* An implant releasing the gonadotropin hormone-releasing hormone agonist histrelin maintains medical castration for up

to 30 months in metastatic prostate cancer. *J Urol (Baltimore)* 2000; **163**: 838–44.
5. Schlegel PN, *et al.* Effective long-term androgen suppression in men with prostate cancer using a hydrogel implant with the GnRH agonist histrelin. *Urology* 2001; **58**: 578–82.
6. Dineen MK, *et al.* An evaluation of the pharmacokinetics and pharmacodynamics of the histrelin implant for the palliative treatment of prostate cancer. *J Clin Pharmacol* 2005; **45**: 1245–9.
7. Schlegel PN, Histrelin Study Group. Efficacy and safety of histrelin subdermal implant in patients with advanced prostate cancer. *J Urol (Baltimore)* 2006; **175**: 1353–8.
8. Schlegel P. A review of the pharmacokinetic and pharmacological properties of a once-yearly administered histrelin acetate implant in the treatment of prostate cancer. *BJU Int* 2009; **103** (suppl 2): 7–13.
9. Crawford ED. A review of the use of histrelin acetate in the treatment of prostate cancer. *BJU Int* 2009; **103** (suppl 2): 14–22.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p. 2254.1). Histrelin acetate has been given by subcutaneous injection in usual doses equivalent to histrelin 10 micrograms/kg daily. Alternatively, a subcutaneous implant containing histrelin acetate 50 mg and designed to release histrelin acetate 65 micrograms daily for 12 months may be used. The implant is not recommended for children under 2 years of age.

References to the use of histrelin.

1. Barradell LB, McTavish D. Histrelin: a review of its pharmacological properties and therapeutic role in central precocious puberty. *Drugs* 1993; **45**: 570–88.
2. Feuillan PP, *et al.* Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. *J Clin Endocrinol Metab* 1999; **84**: 44–9.
3. Klein KO, *et al.* Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; **86**: 4711–16.
4. Hirsch HJ, *et al.* The histrelin implant: a novel treatment for central precocious puberty. Abstract: *Pediatrics* 2005; **116**: 1534–5. Full version: http://pediatrics.aappublications.org/cgi/reprint/116/6/e798 (accessed 04/12/07)
5. Eugster EA, *et al.* Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial. *J Clin Endocrinol Metab* 2007; **92**: 1697–1704.
6. Lewis KA, Eugster EA. Experience with the once-yearly histrelin (GnRHa) subcutaneous implant in the treatment of central precocious puberty. *Drug Des Devel Ther* 2009; **3**: 1–5.
7. Rahhal S, *et al.* Results of a second year of therapy with the 12-month histrelin implant for the treatment of central precocious puberty. *Int J Pediatr Endocrinol* 2009; **2009**: 812517.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1.

Effects on the liver. A report of hepatotoxicity associated with a subcutaneous implant of histrelin acetate.[1]

1. Ricker JM, *et al.* Drug-induced liver injury caused by the histrelin (Vantus) subcutaneous implant. *South Med J* 2010; **103**: 84–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Vantas; *Belg.*: Vantasse; *Canad.*: Vantas; *Cz.*: Vantas; *Denm.*: Vantas; *Fin.*: Vantas; *Ger.*: Vantas; *Irl.*: Vantas; *Malaysia*: Vantas†; *Neth.*: Vantasse; *Norw.*: Vantas; *Pol.*: Vantas; *Singapore*: Vantas; *Spain*: Vantas; *Swed.*: Vantas; *Switz.*: Vantas; *Thai.*: Vantas†; *UK*: Vantas; *Ukr.*: Vantas (Вантас); *USA*: Supprelin; Vantas.

Human Menopausal Gonadotrophins *(BANJ)* ⊗

Gonadotrofina menopáusica humana; Gonadotropina menopáusica humana; HMG; Org-31338; Urogonadotrophin.

ATC — G03GA02.

ATC Vet — QG03GA02.

Description. A purified extract of human postmenopausal urine containing follicle-stimulating hormone (FSH) and luteinising hormone (LH); the relative *in-vivo* activity is expressed as a ratio. Human menopausal gonadotrophins with a ratio of FSH:LH of 1:1 are known as menotrophin (see below).

Menotrophin *(BANJ)* ⊗

Menotrofina; Menotropiini; Menotropin; Menotropina; Menotropins (USAN); Menotropinum.

CAS — 9002-68-0.

UNII — 5Y9QQM372Q.

Pharmacopoeias. In *Br.*, *Chin.*, and *Jpn*.

BP 2014: (Menotrophin). A dry preparation containing glycoprotein gonadotrophins possessing follicle-stimulating and luteinising activities. It contains not less than 40 units of follicle-stimulating hormone activity per mg. The ratio of units of luteinising hormone activity to units of follicle-stimulating hormone activity is about 1. The preparation is exclusively or mainly of pituitary origin and obtained from the urine of postmenopausal women but, when necessary, chorionic gonadotrophin obtained from the urine of pregnant women may be added to achieve the above ratio. An almost white or slightly yellow powder. Soluble in water. Store in airtight containers. Protect from light.

Uses and Administration

Human menopausal gonadotrophins possess both follicle-stimulating hormone (FSH) activity (see p. 2278.2) and luteinising hormone (LH) activity (see p. 2287.1).

Human menopausal gonadotrophins are used in the treatment of male and female infertility due to hypogonadism. In anovulatory infertility unresponsive to clomifene, human menopausal gonadotrophins are given to induce follicular maturation and are followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation, a topic discussed further on p. 2253.1.

The dosage and schedule of treatment for **female infertility** must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or plasma-oestradiol or by ultrasonic visualisation of follicles, or a combination of these. Human menopausal gonadotrophins may be given daily by intramuscular or subcutaneous injection to provide a dose of 75 to 150 units of FSH and gradually adjusted if necessary until an adequate response is achieved. Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units (see p. 2258.1). In menstruating patients treatment should be started within the first 7 days of the menstrual cycle. In the UK it has been suggested that the treatment course should be abandoned if no response is seen in 3 weeks. The course may be repeated at least twice more if necessary. In the USA, licensed product information recommends a maximum daily dose of 450 units and that a course should not exceed 12 days.

An alternative schedule is to give three equal doses by intramuscular or subcutaneous injection, each providing 225 to 375 units of FSH on alternate days followed by chorionic gonadotrophin one week after the first dose.

In IVF and other assisted conception techniques, human menopausal gonadotrophins are used with chorionic gonadotrophin and sometimes also clomifene citrate or a gonadorelin analogue. Stimulation of follicular growth is produced by human menopausal gonadotrophins given by intramuscular or subcutaneous injection, in a dose providing 75 to 300 units of FSH daily, usually beginning on the 2nd or 3rd day of the menstrual cycle. Treatment is continued until an adequate response is obtained and the final injection of human menopausal gonadotrophins is followed 1 to 2 days later with up to 10 000 units of chorionic gonadotrophin. Oocyte retrieval is carried out about 32 to 36 hours later. US licensed product information recommends a starting dose of 225 units daily in women who have undergone pituitary suppression, and a maximum daily dose of 450 units.

In **men with infertility** due to hypogonadotrophic hypogonadism (see Infertility, p. 2253.1), spermatogenesis is stimulated with chorionic gonadotrophin and then human menopausal gonadotrophins are added in a dose of 75 or 150 units of FSH two or three times weekly by intramuscular or subcutaneous injection. Treatment should be continued for at least 3 or 4 months.

Infertility. Systematic reviews initially found no evidence of a significant difference in efficacy for human menopausal gonadotrophins compared with urinary-derived gonadotrophins in women with anovulatory infertility[1] (p. 2253.1), or compared with recombinant follicle-stimulating hormone in assisted reproduction cycles.[2] However, it has since been suggested that there is evidence of an improved live-birth rate when human menopausal gonadotrophins are used in current IVF protocols rather than follicle-stimulating hormone.[3,4] UK guidelines suggest that either urinary or recombinant gonadotrophins may be used during controlled ovarian stimulation in IVF treatment.[5]

1. Nugent D, *et al.* Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 16/09/05).
2. Van Wely M, *et al.* Human menopausal gonadotropin versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/09/05).
3. Coomarasamy A, *et al.* Urinary hMG versus recombinant FSH for controlled ovarian hyperstimulation following an agonist long down-regulation protocol in IVF or ICSI treatment: a systematic review and meta-analysis. *Hum Reprod* 2008; **23**: 310–15.
4. Afnan M. Identifying real differences in live birth rates between HMG and rFSH in IVF. *Reprod Biomed Online* 2009; **18** (suppl 2): 25–30.
5. NICE. Fertility: assessment and treatment for people with fertility problems (issued February 2013). Available at: http://www.nice.org.uk/nicemedia/live/14078/62769/62769.pdf (accessed 30/10/13)

Adverse Effects

Human menopausal gonadotrophins may cause dose-related ovarian hyperstimulation varying from mild ovarian enlargement and abdominal discomfort to severe hyperstimulation with marked ovarian enlargement or cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock and thromboembolic disorders. Rupture of ovarian cysts and intraperitoneal haemorrhage has occurred, usually after pelvic examination. Fatalities have been reported.

Hypersensitivity reactions and local reactions at the injection site may occur. Nausea and vomiting, joint pains and fever have been reported; gynaecomastia, acne, and weight gain have occurred in men.

Carcinogenicity. In a case-control study of 4575 women with primary invasive breast cancer, an evaluation of risk factors found that, overall, the use of infertility drugs was not associated with an increased risk of breast cancer.[1] However, subgroup analysis of individual drugs found that the use of human menopausal gonadotrophins for at least 6 months or 6 treatment cycles was associated with a risk of breast cancer that was 2 to 3 times greater than for women who had never received any fertility treatment. The authors of this study noted that these results were based on small numbers and that other studies had failed to show an association between fertility treatment and breast cancer.

1. Burkman RT, *et al.* Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study. *Fertil Steril* 2003; **79**: 844–51.

Effects on the ovary. Ovarian hyperstimulation syndrome after use of human menopausal gonadotrophins in 4 women progressed to acute adnexal torsion.[1] Deep-vein thrombosis has also been a rare complication of ovarian hyperstimulation syndrome associated with the use of human menopausal gonadotrophins plus chorionic gonadotrophin.[2,3] In another case in which thrombosis followed the use of human menopausal gonadotrophins alone, hereditary activated protein C resistance and smoking may have been contributing factors.[4]

1. Kemmann E, *et al.* Adnexal torsion in menotropin-induced pregnancies. *Obstet Gynecol* 1990; **76**: 403–6.
2. Kaaja R, *et al.* Severe ovarian hyperstimulation syndrome and deep venous thrombosis. *Lancet* 1989; **ii**: 1043.
3. Sobande AA, *et al.* Ovarian hyperstimulation syndrome and deep vein thrombosis. *Saudi Med J* 2000; **21**: 783–4.
4. Ludwig M, *et al.* Deep vein thrombosis during administration of HMG for ovarian stimulation. *Arch Gynecol Obstet* 2000; **263**: 139–41.

Precautions

Human menopausal gonadotrophins should not be given to pregnant patients. Use should be avoided in patients with abnormal genital bleeding, hormone sensitive malignancies such as those of the breast, uterus, prostate, ovaries or testes, or ovarian cysts or enlargement not caused by the polycystic ovary syndrome. Pituitary or hypothalamic lesions, adrenal or thyroid disorders, and hyperprolactinaemia should be treated appropriately to exclude them as causes of infertility before attempting therapy with human menopausal gonadotrophins. Patients who have ovarian enlargement are at risk of rupture; pelvic examinations should be avoided or carried out with care and the recommendation has been made that sexual intercourse should be avoided while there is such a risk.

There is a risk of multiple births.

Interactions

In women who show evidence of excessive ovarian stimulation while receiving human menopausal gonadotrophins the use of drugs with luteinising-hormone (LH) activity increases the risk of ovarian hyperstimulation syndrome.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: HMG Perring; Lifecell; Menopur; *Austral.*: Humegon†; Menopur; *Austria*: Menopur; *Belg.*: Menopur; *Braz.*: Merional-HMG; Pergonal†; *Canad.*: Menopur; Repronex; *Chile*: Menopur; *China*: Lebaode (乐宝得); Menopur (贺美奇); *Cz.*: Menogon; Menopur; Merional; *Denm.*: Menopur; *Fin.*: Menopur; *Fr.*: Menopur; *Ger.*: Menogon; *Gr.*: Altermon; Humegon; Menogon; Menopur; Merional; Pergogreen; Pergonal; *Hong Kong*: Menogon; Menopur; Merional†; Pergonal†; *Hung.*: Menopur; Merional; *India*: Eventin; Fergonad-M; Follilutin; Follinis; GMH; Gynogen; Humegon; Humog; IVF-M; Materna HMG; Menodac; Menogon; Menolife; Menonys; Menopur; Menotec; Menovul; Ovugraf-HP; Ovulate-M; Pergonal; Pregnorm; *Irl.*: Humegon†; Menopur; *Israel*: Menogon; Menopur; *Ital.*: Menogon; Meropur; *Jpn*: Gonadorylt; *Malaysia*: Menopur; *Mex.*: Merapur HP; Merional; *Neth.*: Menogon†; Menopur; *Norw.*: Menopur; *Philipp.*: Menogon; *Pol.*: Menopur; Merional; *Port.*: Menopur; *Rus.*: Menogon

(Меногон)†; Menopur (Менопур); Pergonal (Пергонал); *S.Afr.*: Menopur; *Singapore*: Menogon; Menopur; *Spain*: HMG; Menopur; *Swed.*: Menopur; *Switz.*: Menopur; Merional; *Thai.*: IVF-M; Menogon; Menopur; *Turk.*: Humegon; Menogon; Menopur; Merional; Pergonal; *UK*: Menopur; Merional; *Ukr.*: Menogon (Меногон); Menopur (Менопур); Merional (Мериональ); *USA*: Humegon†; Menopur; Repronex.

Pharmacopoeial Preparations
BP 2014: Menotrophin Injection.

Hydroxyestrone Diacetate

Hidroxiestrona, diacetato de; 16α-Hydroxyoestrone Diacetate.
3,16α-Dihydroxyestra-1,3,5(10)-trien-17-one diacetate.
$C_{22}H_{26}O_5$=370.4
CAS — 566-76-7 (hydroxyestrone); 1247-71-8 (hydroxyestrone diacetate).

Profile

Hydroxyestrone diacetate is an oestrogen (see Estradiol, p. 2271.1). It has been given in vulvovaginal disorders and for female infertility.

Hydroxyprogesterone Caproate
(BANM, rINN)

17-AHPC; Caproate d'Hydroxyprogestérone; Caproato de hidroxiprogesterona; Hidroksiprogesteron Heksanoat; Hidroksiprogesteron Kaproat; Hidroxiprogesterona, caproato de; Hydroxyprogesterone Hexanoate; Hydroxyprogesteroni Caproas; NSC-17592; Гидроксипрогестерона Капроат.
3,20-Dioxopregn-4-en-17α-yl hexanoate; 17α-Hydroxypregn-4-ene-3,20-dione hexanoate.
$C_{27}H_{40}O_4$=428.6
CAS — 68-96-2 (hydroxyprogesterone); 630-56-8 (hydroxyprogesterone caproate).
ATC — G03DA03.
ATC Vet — QG03DA03.
UNII — 276F2O42F5.

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

USP 36: (Hydroxyprogesterone Caproate). A white or creamy-white, crystalline powder. Odourless or having a slight odour. Insoluble in water; soluble in ether; slightly soluble in benzene. Protect from light. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Hydroxyprogesterone caproate is a progestogen structurally related to progesterone (p. 2300.2) that may be given to reduce the risk of recurrent miscarriage and of premature birth (see Premature Labour, below). It has also been used, often with an oestrogen, in the management of various menstrual disorders such as oligomenorrhoea or amenorrhoea (p. 2251.3), and dysmenorrhoea (p. 8.2).

In the prevention of recurrent miscarriage associated with proven progesterone deficiency, doses of 250 to 500 mg weekly by intramuscular injection have been given during the first half of pregnancy.

Hydroxyprogesterone caproate may also be used to reduce the risk of premature birth in women with a singleton pregnancy who have a history of singleton spontaneous premature delivery. A dose of 250 mg is given by deep intramuscular injection once weekly, starting between 16 weeks 0 days, and 20 weeks 6 days, of gestation. Treatment is continued until the start of week 37 or delivery, whichever occurs first.

In the management of menstrual disorders, a single intramuscular dose of hydroxyprogesterone caproate 250 mg has been given sometime between days 16 and 20 of the menstrual cycle.

The acetate and the enantate have also been used.

Premature labour. In women who have a history of spontaneous premature delivery (p. 2131.1), there is some evidence to suggest that prophylactic progesterone may reduce the risk for premature delivery in subsequent pregnancies.[1,2] Most studies have used vaginal progesterone formulations or intramuscular hydroxyprogesterone caproate, generally starting around week 16 to 20 of gestation and continuing through to week 36 or delivery. In women with a singleton pregnancy, who have a history of spontaneous premature delivery, prophylactic therapy can reduce the risk of perinatal death and of preterm delivery (before 34 weeks of gestation). Neonatal benefits include a reduction in the risks of low birth-weight (less than 2.5 kg), morbidity including necrotising enterocolitis, the need for assisted ventilation, and neonatal death. Preterm birth has also been reduced in women at risk because of a short cervix, although less information is available about other maternal and neonatal outcomes in this group. The effects of prophylactic therapy in women with other risk factors for premature delivery, and those presenting with threatened premature labour, are uncertain, although there is limited evidence to suggest that the risk of infant birth-weight less than 2.5 kg may be reduced. However, prophylactic therapy does not appear to be of benefit in multiple gestations. Overall, further study is required, particularly to identify the optimal timing, route, and dose of treatment, and long-term effects on infant health.[2]

An expert committee in the USA has recommended[3] that progesterone or hydroxyprogesterone caproate should be offered to women with a singleton pregnancy and a history of spontaneous preterm singleton delivery, starting at 16 to 24 weeks of gestation. It also recommended the use of vaginal progesterone as an option for women with a singleton pregnancy, without a history of preterm birth, who have a short cervix (20 mm or less) before or at 24 weeks of gestation. In Canada,[4] a history of preterm labour is considered an indication for intramuscular hydroxyprogesterone caproate 250 mg weekly, or vaginal progesterone 100 mg daily, given from 20 weeks of gestation until the risk of prematurity is low. For women with a short cervix (less than 15 mm at 22 to 26 weeks of gestation), vaginal progesterone 200 mg daily may be used.

1. Schmouder VM, *et al.* The rebirth of progesterone in the prevention of preterm labor. *Ann Pharmacother* 2013; 47: 527–36.
2. Dodd JM, *et al.* Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2013 (accessed 26/11/13).
3. American College of Obstetricians and Gynecologists. Practice bulletin 130: prediction and prevention of preterm birth. *Obstet Gynecol* 2012; 120: 964–73.
4. Farine D, *et al.* Society of Obstetricians and Gynaecologists of Canada. The use of progesterone for prevention of preterm birth. *J Obstet Gynaecol Can* 2008; 30: 67–71. Also available at: http://www.sogc.org/guidelines/documents/guiJOGC202TU0801.pdf (accessed 03/12/13)

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3).

There may be local reactions at the site of injection. Rarely, coughing, dyspnoea, and circulatory disturbances may occur during or immediately after injection of hydroxyprogesterone caproate but can be avoided by injecting the drug very slowly.

Pregnancy. Abnormalities reported in infants born to mothers who had received hydroxyprogesterone during pregnancy have included tetralogy of Fallot in one infant,[1] genito-urinary abnormalities in 2 infants,[2] and adrenocortical carcinoma in one infant.[3]

1. Heinonen OP, *et al.* Cardiovascular birth defects and antenatal exposure to female sex hormones. *N Engl J Med* 1977; 296: 67–70.
2. Evans ANW, *et al.* The ingestion by pregnant women of substances toxic to the foetus. *Practitioner* 1980; 224: 315–19.
3. Mann JR, *et al.* Transplacental carcinogenesis (adrenocortical carcinoma) associated with hydroxyprogesterone hexanoate. *Lancet* 1983; ii: 580.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2).

Pharmacokinetics

After a single intramuscular dose of 1 g, peak serum concentrations of hydroxyprogesterone caproate occur in 3 to 7 days, and the elimination half-life is about 7.8 days. Hydroxyprogesterone caproate is highly bound to plasma proteins. It is extensively metabolised, mainly via the cytochrome P450 isoenzymes CYP3A4 and CYP3A5. Both conjugated metabolites and free steroids are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gestageno; Proluton Depot; *Austria*: Proluton Depot; *Cz.*: Neolutin Forte; *Fr.*: Progesterone-retard Pharlon; *Ger.*: Progesteron-Depot†; Proluton Depot†; *Gr.*: Proluton Depot; *India*: Anin; Arisafe; Darvon; Depovig; Fetugest; Gestaur; Gestimax; Gynonys; Hiprogress; HPC Depot; Hylex; Hyprogres; Hyprosafe; LGP-H; Maintane; Maloxy; Novadepot; NT-Natal; Nunest; Proluton Depot; *Ital.*: Lentogest; Proluton; *Malaysia*: Hiprogin; Proluton Depot; *Mex.*: Capostent†; Primolut Depot; *Philipp.*: Proluton Depot†; *Pol.*: Kaprogest†; *Thai.*: Proluton Depot; *Turk.*: Proluton Depot; *USA*: Makena.

Multi-ingredient Preparations. *Arg.*: Dos Dias N; Primosiston; *Braz.*: Gestadinona; Trinestril; *Mex.*: Gravidinona.

Pharmacopoeial Preparations
USP 36: Hydroxyprogesterone Caproate Injection.

Leuprorelin *(BAN, rINN)* ⊗

Leuprolide; Leuprorelini; Leuprorelina; Leuprorelinas; Leuproréline; Leuprorelinum; Лейпрорелин.
5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide.
$C_{59}H_{84}N_{16}O_{12}$=1209.4
CAS — 53714-56-0.
ATC — L02AE02.
ATC Vet — QL02AE02.
UNII — EFY6W0M8TG.

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

Ph. Eur. 8: (Leuprorelin). A synthetic nonapeptide analogue of the hypothalamic peptide gonadorelin. It is obtained by chemical synthesis and is available as an acetate. A white or almost white, hygroscopic, powder. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Leuprorelin Acetate *(BANM, rINNM)* ⊗

Abbott-43818; Acetato de leuprorelina; Leuprolide Acetate (USAN); Leuprorelinasetaatti; Leuprorelina, acetato de; Leuprorelinacetat; Leuproréline, Acétate de; Leuprorelini Acetas; Löprorelin Asetat; TAP-144; Лейпрорелина Ацетат.
$C_{59}H_{84}N_{16}O_{12},C_2H_4O_2$=1269.5
CAS — 74381-53-6.
ATC — L02AE02.
ATC Vet — QL02AE02.
UNII — 37JNS02E7V.

Pharmacopoeias. In *US.*

USP 36: (Leuprolide Acetate). Store in airtight containers at a temperature not exceeding 30 degrees.

Uses and Administration

Leuprorelin is an analogue of gonadorelin (p. 2280.3) with similar properties. Continuous administration is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate; it may also be used in the treatment of breast cancer in premenopausal women. In the management of endometriosis, leuprorelin may be used for pain relief and endometrial reduction, and for preparation before endometrial ablation or resection. It may also be used preoperatively to reduce the size of uterine fibroids and associated bleeding. For its use in precocious puberty, see p. 2286.2. Leuprorelin has also been given in other sex-hormone-related disorders. It is used as the acetate.

In the palliative treatment of **advanced prostate cancer**, leuprorelin acetate may be given by subcutaneous injection in a usual single daily dose of 1 mg. It is also given subcutaneously or intramuscularly as depot preparations but the dosage and route of these may differ between countries. In the USA, the dose is 7.5 mg monthly, 22.5 mg every 3 months, 30 mg every 4 months, or 45 mg every 6 months, given subcutaneously or intramuscularly, depending on the preparation. In the UK, leuprorelin acetate may also be used in advanced prostate cancer, as well as medical treatment of locally advanced cancer, as an adjuvant to surgery in locally advanced cancer at high risk of progression, or as an adjuvant to radiotherapy in high-risk localised or locally advanced disease. A dose of 3.75 mg may be given once a month, by subcutaneous or intramuscular injection, or 11.25 mg may be given subcutaneously every 3 months. A nonbiodegradable titanium alloy implant, which was inserted subcutaneously into the inner part of the upper arm, was also available in the USA for advanced disease. It contained 72 mg of leuprorelin acetate and delivered the drug at a controlled rate of 120 micrograms daily for 12 months. An anti-androgen such as cyproterone acetate may be given for several days before beginning leuprorelin therapy and continued for about 3 weeks, to avoid the risk of a disease flare.

Depot injections of leuprorelin acetate may also be used for hormonal therapy in the management of **breast cancer**; for example, subcutaneous doses of 3.75 mg monthly, or 11.25 mg once every 3 months, may be given.

For the management of **endometriosis**, leuprorelin acetate 3.75 mg may be given as a monthly depot injection intramuscularly or subcutaneously, depending on the preparation. Alternatively, 11.25 mg may be given as an intramuscular depot every 3 months. Treatment is started during the first 5 days of the menstrual cycle, and may be continued for up to 6 months. To prepare for uterine surgery such as endometrial ablation or resection, a single 3.75 mg depot injection may be given 5 to 6 weeks before the procedure.

When used for pre-operative management of **uterine fibroids**, leuprorelin is usually given for about 3 months, but may be continued for up to 6 months. Leuprorelin acetate 3.75 mg may be given as a monthly depot injection

intramuscularly or subcutaneously, depending on the preparation. Alternatively, a single intramuscular 3-month depot dose of 11.25 mg may be used.

General references.
1. Plosker GL, Brogden RN. Leuprorelin: a review of its pharmacology and therapeutic use in prostatic cancer, endometriosis and other sex hormone-related disorders. *Drugs* 1994; **48**: 930–67.
2. Wilson AC, *et al.* Leuprolide acetate: a drug of diverse clinical applications. *Expert Opin Invest Drugs* 2007; **16**: 1851–63.

Administration in children. Leuprorelin may be used in the management of central precocious puberty—see below.

Benign prostatic hyperplasia. For a discussion of the management of benign prostatic hyperplasia, including mention of the use of gonadorelin analogues and the view that they are unsatisfactory for indefinite therapy, see p. 2347.1.

References to the use of leuprorelin.

1. Gabrilove JL, *et al.* Effect of long-acting gonadotropin-releasing hormone analog (leuprolide) therapy on prostatic size and symptoms in 15 men with benign prostatic hypertrophy. *J Clin Endocrinol Metab* 1989; **69**: 629–32.
2. Eri LM, Tveter KJ. A prospective, placebo-controlled study of the luteinizing hormone-releasing hormone agonist leuprolide as treatment for patients with benign prostatic hyperplasia. *J Urol (Baltimore)* 1993; **150**: 359–64.
3. Eri LM, Tveter KJ. Safety, side effects and patient acceptance of the luteinizing hormone releasing hormone agonist leuprolide in treatment of benign prostatic hyperplasia. *J Urol (Baltimore)* 1994; **152**: 448–52.
4. Eri LM, *et al.* Effects on the endocrine system of long-term treatment with the luteinizing hormone-releasing hormone agonist leuprolide in patients with benign prostatic hyperplasia. *Scand J Clin Lab Invest* 1996; **56**: 319–25.

Disturbed behaviour. Leuprorelin has been used in the treatment of men with paraphilias (p. 1030.2). Case series have reported reductions in abnormal sexual thoughts and behaviours.[1-3]

1. Briken P, *et al.* Treatment of paraphilia with luteinizing hormone-releasing hormone agonists. *J Sex Marital Ther* 2001; **27**: 45–55.
2. Krueger RB, Kaplan MS. Depot-leuprolide acetate for treatment of paraphilias: a report of twelve cases. *Arch Sex Behav* 2001; **30**: 409–22.
3. Saleh FM, *et al.* Treatment of paraphilia in young adults with leuprolide acetate: a preliminary case report series. *J Forensic Sci* 2004; **49**: 1343–8.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p. 2264.1) but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' hormone replacement therapy can be used to prevent this.

References to the use of leuprorelin.

1. Hornstein MD, *et al.* Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Obstet Gynecol* 1998; **91**: 16–24.
2. Ling FW. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. *Obstet Gynecol* 1999; **93**: 51–8.
3. Takeuchi H, *et al.* A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis. *J Obstet Gynaecol Res* 2000; **26**: 325–31.
4. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol* 2002; **99**: 709–19.
5. Rotondi M, *et al.* Depot leuprorelin acetate versus danazol in the treatment of infertile women with symptomatic endometriosis. *Eur J Gynaecol Oncol* 2002; **23**: 523–6.
6. Schlaff WD, *et al.* Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. *Fertil Steril* 2006; **85**: 314–25.
7. Bedaiwy MA, Casper RF. Treatment with leuprolide acetate and hormonal add-back for up to 10 years in stage IV endometriosis patients with chronic pelvic pain. *Fertil Steril* 2006; **86**: 220–2.

Fibroids. Gonadorelin analogues may be of some benefit as an adjunct or alternative to surgery in women with uterine fibroids (p. 2281.2), although there has been some concern that this might complicate the diagnosis of malignancy.

References to the use of leuprorelin.

1. Friedman AJ, *et al.* Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. *Obstet Gynecol* 1991; **77**: 720–5.
2. Friedman AJ, *et al.* Long-term medical therapy for leiomyomata uteri: a prospective, randomized study of leuprolide acetate depot plus either oestrogen-progestin or progestin 'add-back' for 2 years. *Hum Reprod* 1994; **9**: 1618–25.
3. Zullo F, *et al.* A prospective randomized study to evaluate leuprolide acetate treatment before laparoscopic myomectomy: efficacy and ultrasonographic predictors. *Am J Obstet Gynecol* 1998; **178**: 108–112.
4. Scialli AR, Levi AJ. Intermittent leuprolide acetate for the nonsurgical management of women with leiomyomata uteri. *Fertil Steril* 2000; **74**: 540–6.
5. Jasonni VM, *et al.* Randomized double-blind study evaluating the efficacy on uterine fibroids shrinkage and on intra-operative blood loss of different length of leuprolide acetate depot treatment before myomectomy. *Acta Obstet Gynecol Scand* 2001; **80**: 956–8.

Hirsutism. The mainstay of drug treatment for hirsutism (p. 2262.1) has been an anti-androgen, usually cyproterone acetate or spironolactone. Although gonadorelin analogues have been used, and are effective, they must be given parenterally or nasally and may produce menopausal effects, notably osteoporosis.

References to the use of leuprorelin.

1. Elkind-Hirsch KE, *et al.* Combination gonadotropin-releasing hormone agonist and oral contraceptive therapy improves treatment of hirsute women with ovarian hyperandrogenism. *Fertil Steril* 1995; **63**: 970–8.
2. Azziz R, *et al.* Leuprolide and estrogen versus oral contraceptive pills for the treatment of hirsutism: a prospective randomized study. *J Clin Endocrinol Metab* 1995; **80**: 3406–11.
3. Ciotta L, *et al.* Clinical and hormonal effects of gonadotropin-releasing hormone agonist plus an oral contraceptive in severely hirsute patients with polycystic ovary disease. *Fertil Steril* 1996; **65**: 61–7.
4. Bayhan G, *et al.* A comparative study of a gonadotropin-releasing hormone agonist and finasteride on idiopathic hirsutism. *Clin Exp Obstet Gynecol* 2000; **27**: 203–6.

Infertility. Gonadorelin analogues are used in the treatment of infertility—see p. 2253.1.

References to the use of leuprorelin.

1. Stone BA, *et al.* Gonadotrophin and estradiol levels during ovarian stimulation in women treated with leuprolide acetate. *Obstet Gynecol* 1989; **73**: 990–5.
2. Sathanandan M, *et al.* Adjuvant leuprolide in normal, abnormal, and poor responders to controlled ovarian hyperstimulation for in vitro fertilization/gamete intrafallopian transfer. *Fertil Steril* 1989; **51**: 998–1006.
3. Filicori M, *et al.* Different gonadotropin and leuprorelin ovulation induction regimens markedly affect follicular fluid hormone levels and folliculogenesis. *Fertil Steril* 1996; **65**: 387–93.
4. Surrey ES, *et al.* Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients with endometriosis. *Fertil Steril* 2002; **78**: 699–704.

Malignant neoplasms. Gonadorelin analogues are used as an alternative to orchidectomy in the management of advanced malignant neoplasms of the prostate (p. 712.3). Such therapy is as effective as orchidectomy in prolonging survival;[1] combination of leuprorelin or other gonadorelin analogues with nonsteroidal anti-androgens to produce maximal androgen blockade produces only modest additional benefit.[2] Intermittent maximal androgen blockade is being studied in an attempt to improve results, and leuprorelin is also under investigation as neoadjuvant therapy in localised disease.[3] Leuprorelin is also used for ovarian ablation[4] in premenopausal women with breast cancer (p. 702.1).

There are isolated reports of endometrial cancer[5] and ovarian cancer[6] responding to leuprorelin, but the role of the gonadorelin analogues in these conditions is much less well established.

1. Seidenfeld J, *et al.* Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; **132**: 566–77.
2. Prostate Cancer Tnalists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000; **355**: 1491–8.
3. Persad R. Leuprorelin acetate in prostate cancer: a European update. *Int J Clin Pract* 2002; **56**: 389–96.
4. Schmid P, *et al.* Cyclophosphamide, methotrexate and fluorouracil (CMF) versus hormonal ablation with leuprorelin acetate as adjuvant treatment of node-positive, premenopausal breast cancer patients: preliminary results of the TABLE-study (Takeda Adjuvant Breast cancer study with Leuprorelin Acetate). *Anticancer Res* 2002; **22**: 2325–32.
5. Noci I, *et al.* Longstanding survival without cancer progression in a patient affected by endometrial carcinoma treated primarily with leuprolide. *Br J Cancer* 2001; **85**: 333–6.
6. Paskeviciute L, *et al.* No rules without exception: long-term complete remission observed in a study using a LH-RH agonist in platinum-refractory ovarian cancer. *Gynecol Oncol* 2002; **86**: 297–301.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p. 2254.1). Leuprorelin may be used, although the dosages and routes of administration can vary between products in different countries. In the USA, leuprorelin acetate may be given by intramuscular depot injection once every month in the following initial doses according to weight:

- up to 25 kg: 7.5 mg
- 25 to 37.5 kg: 11.25 mg
- more than 37.5 kg: 15 mg

The dose should be adjusted according to response, and may be titrated upwards in steps of 3.75 mg at the next monthly dose. Depot injections containing 11.25 mg or 30 mg for intramuscular use once every 3 months are also available.

Leuprorelin acetate has also been given in a dose of 50 micrograms/kg daily by subcutaneous injection. This should be adjusted according to response, and may be titrated upwards in steps of 10 micrograms/kg daily.

Although leuprorelin is not licensed for use in children in the UK, the *BNFC* includes a dose of 3.75 mg, given once every 4 weeks as a subcutaneous or intramuscular depot injection; this dose may be halved for children weighing less than 20 kg. Alternatively, a dose of 11.25 mg may be given once every 12 weeks.

References to the use of leuprorelin.

1. Carel J-C, *et al.* Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25 mg). *J Clin Endocrinol Metab* 2002; **87**: 4111–16.
2. Tanaka T, *et al.* Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function: the TAP-144-SR Japanese Study Group on Central Precocious Puberty. *J Clin Endocrinol Metab* 2005; **90**: 1371–6.
3. Neely EK, *et al.* Leuprolide acetate 1-month depot for central precocious puberty: hormonal suppression and recovery. *Int J Pediatr Endocrinol* 2010; **2010**: 398639.
4. Lee PA, *et al.* Efficacy of leuprolide acetate 1-month depot for central precocious puberty (CPP): growth outcomes during a prospective, longitudinal study. *Int J Pediatr Endocrinol* 2011; **2011**: 7.
5. Jaruratanasirikul S, Thaiwong M. Outcome of gonadotropin-releasing analog treatment for children with central precocious puberty: 15-year experience in southern Thailand. *J Pediatr Endocrinol Metab* 2011; **24**: 519–23.
6. Lee PA, *et al.* Efficacy and safety of leuprolide acetate 3-month depot 11.25 milligrams or 30 milligrams for the treatment of central precocious puberty. *J Clin Endocrinol Metab* 2012; **97**: 1572–80.

Premenstrual syndrome. For reference to the use of leuprorelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug therapy, see under Gonadorelin, p. 2281.3.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1. Thrombocytopenia and leucopenia have been reported rarely.

Benign intracranial hypertension. Increased intracranial pressure associated with leuprorelin treatment has been reported in a few isolated cases.[1,2]

1. Arbet N, *et al.* Pseudotumor cerebri associated with leuprorelin acetate. *Lancet* 1990; **335**: 668.
2. Boot JH. Pseudotumour cerebri as a side effect of leuprorelin acetate. *Ir J Med Sci* 1996; **165**: 60.

Effects on the eyes. Leuprorelin may be associated with blurred vision, usually lasting 1 to 2 hours after injection, but in rare instances longer.[1] Haemorrhage or occlusion of intra-ocular blood vessels, ocular pain, and lid oedema have also been reported but the association is less well established.

1. Fraunfelder FT, Edwards R. Possible ocular adverse effects associated with leuprolide injections. *JAMA* 1995; **273**: 773–4.

Effects on the liver. A report of hepatotoxicity associated with the use of leuprorelin.[1]

1. Gabbi C, *et al.* Nonalcoholic fatty liver disease induced by leuprorelin acetate. *J Clin Gastroenterol* 2008; **42**: 107–10.

Hypersensitivity. An anaphylactic reaction started within 5 minutes of the injection of a leuprorelin depot formulation in a patient with prostate cancer.[1] Recurrent anaphylaxis developed in another patient given a depot injection of leuprorelin acetate for endometriosis, requiring both acute and chronic management.[2]

1. Taylor JD. Anaphylactic reaction to LHRH analogue, leuprorelin. *Med J Aust* 1994; **161**: 455.
2. Letterie GS, *et al.* Recurrent anaphylaxis to a depot form of GnRH analogue. *Obstet Gynecol* 1991; **78**: 943–6.

Local reactions. Local reactions, including erythema, pain, induration, granulomas, and sterile abscess are particularly associated with depot injections of gonadorelin analogues such as leuprorelin and triptorelin;[1-9] they may also occur with subcutaneous daily injection.[1] It has been suggested that the depot vehicle, a lactic acid-glycolic acid copolymer, may be responsible for many, although not all, such reactions.[1-5] Reactions are claimed to be more prevalent in children than in adults;[4] an incidence of about 5% of patients has been suggested. Reactions are apparently idiosyncratic and may occur at any time during therapy, may be intermittent, or may never recur.[4]

1. Manasco PK, *et al.* Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; **123**: 334–5.
2. Neely EK, *et al.* Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; **123**: 335.
3. Tonini G, *et al.* Local reactions to luteinizing hormone releasing hormone analog therapy. *J Pediatr* 1995; **126**: 159.
4. Neely EK, *et al.* Local reactions to luteinizing hormone releasing hormone analog therapy. *J Pediatr* 1995; **126**: 159–60.
5. Yasukawa K, *et al.* Leuprorelin acetate granulomas: case reports and review of the literature. *Br J Dermatol* 2005; **152**: 1045–7.
6. Dangle P, *et al.* Noninfective cutaneous granuloma with leuprorelin acetate—reality or myth. *Urology* 2007; **69**: 779.e5–6.
7. Shiota M, *et al.* Injection-site granulomas resulting from the administration of both leuprorelin acetate and goserelin acetate for the treatment of prostatic cancer. *J Nippon Med Sch* 2007; **74**: 306–8.
8. Vieu C, *et al.* Granulome sur le site d'injection de leuproréline retard: réaction à corps étranger à l'excipient? *Ann Dermatol Venereol* 2007; **134**: 771–3.
9. Watanabe T, *et al.* A morphological study of granulomas induced by subcutaneous injection of leuprorelin acetate. *J Cutan Pathol* 2009; **36**: 1299–1302.

Pituitary apoplexy. Pituitary apoplexy occurred shortly after the injection of a depot formulation of leuprorelin for the treatment of prostate cancer in 2 patients with occult pituitary adenomas.[1,2] In a woman receiving leuprorelin daily in preparation for oocyte donation, symptoms began after the third dose.[3] Signs and symptoms in these cases included headache, visual disturbances, generalised weakness, nausea and vomiting, and haemorrhagic necrosis of the macroadenoma.

1. Morsi A, *et al.* Pituitary apoplexy after leuprolide administration for carcinoma of the prostate. *Clin Endocrinol (Oxf)* 1996; **44**: 121–4.
2. Reznik Y, *et al.* Pituitary apoplexy of a gonadotroph adenoma following gonadotrophin releasing hormone agonist therapy for prostatic cancer. *J Endocrinol Invest* 1997; **20**: 566–8.
3. Engel G, *et al.* Pituitary apoplexy after leuprolide injection for ovum donation. *J Adolesc Health* 2003; **32**: 89–93.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies leuprorelin 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 06/10/11)

Interactions

As for Gonadorelin, p. 2282.2.

Pharmacokinetics

Leuprorelin acetate is not active when given orally but is well absorbed on subcutaneous or intramuscular injection. After a parenteral dose it has an elimination half-life of about 3 hours.

References.

1. Sennello LT, *et al.* Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. *J Pharm Sci* 1986; 75: 158–60.
2. Periti P, *et al.* Clinical pharmacokinetics of depot leuprorelin. *Clin Pharmacokinet* 2002; 41: 485–504.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Eligard; Lectrum; Leprid; Lupron; *Austral.*: Eligard; Lucrin; *Austria*: Eligard; Enantone; Sixantone; Trenantone; *Belg.*: Depo-Eligard; Lucrin; *Braz.*: Eligard; Lectrum; Lorelin; Lupron; Reliser†; *Canad.*: Eligard; Lupron; *Chile*: Eligard; Lupron; *China*: Enantone (抑那通); *Cz.*: Eligard; Lucrin; *Denm.*: Eligard; Procren; Prostap†; *Fin.*: Eligard; Enanton; Procren; *Fr.*: Eligard; Enantone; *Ger.*: Eligard; Enantone-Gyn; Enantone; Leupro-Sandoz†; Leuprone†; Sixantone; Trenantone; *Gr.*: Daronda; Elityran; Leuprol; *Hong Kong*: Enantone; Lorelin; *Hung.*: Eligard; Lucrin; *India*: Eligard; Leuprofact; Lucrin; Lupride; *Indon.*: Endrolin; Lectrum; Tapros; *Irl.*: Eligard; Prostap; *Israel*: Eligard†; Lucrin; *Ital.*: Eligard; Enantone; *Jpn*: Leuplin; Lupron†; *Malaysia*: Lucrin; *Mex.*: Lectrum; Lorelin; Lucrin; Prelar; Prostide; *Neth.*: Daronda†; Eligard; Lucrin; *Norw.*: Eligard; Enanton; Procren; *NZ*: Eligard; Lucrin; *Philipp.*: Luphere; Luprolex; *Pol.*: Eligard; Lucrin Depot; *Port.*: Eligard; Lucrin; *Rus.*: Eligard (Элигард); Lucrin (Люкрин); *S.Afr.*: Lucrin†; *Singapore*: Lucrin; *Spain*: Eligard; Ginecrin; Lutrate; Procrin; *Swed.*: Eligard; Enanton; Procren; *Switz.*: Eligard; Lucrin; *Thai.*: Enantone; *Turk.*: Lucrin; *UK*: Prostap; *Ukr.*: Eligard (Элигард); *USA*: Eligard; Lupron; *Venez.*: Lupron.

Multi-ingredient Preparations. *USA*: Lupaneta Pack.

Pharmacopoeial Preparations
BP 2014: Leuprorelin Injection.

Luteinising Hormone ⊗

Gonadotropina luteinizante; Hormona luteinizante; Human Interstitial-cell-stimulating Hormone; ICSH; LH; Lutropin; Lutropina.

CAS — 9002-67-9; 39341-83-8 (human).

Lutropin Alfa (BAN, USAN, rINN) ⊗

Lutropina alfa; Lutropine Alfa; Lutropinum Alfa; Лутропин Альфа.

CAS — 152923-57-4 (lutropin alfa); 56832-30-5 (α subunit); 53664-53-2 (β subunit).
ATC — G03GA07.
ATC Vet — QG03GA07.
UNII — 3JGY52XJNA.

Units

35 units of human pituitary luteinising hormone are contained in about 5.8 micrograms (with 1 mg of human albumin, 5 mg of mannitol, and 1 mg of sodium chloride) in one ampoule of the second International Standard (1988).

10 units of the alpha subunit of human pituitary luteinising hormone are contained in about 10 micrograms (with 500 micrograms of human albumin, 2.5 mg of lactose, and 45 micrograms of sodium chloride) in one ampoule of the first International Standard (1984).

10 units of the beta subunit of human pituitary luteinising hormone are contained in 10 micrograms (with 500 micrograms of human albumin, 2.5 mg of lactose, and 45 micrograms of sodium chloride) in one ampoule of the first International Standard (1984).

189 units of recombinant human luteinising hormone are contained in about 8.8 micrograms (with 2 mg of human albumin, 10 mg of lactose, and 8.9 mg of sodium chloride) in one ampoule of the first International Standard (2003).

Uses and Administration

Luteinising hormone (LH) is secreted with follicle-stimulating hormone (FSH) (p. 2278.2), another gonadotrophin, by the anterior pituitary lobe.

These gonadotrophins stimulate the normal functioning of the gonads and the secretion of sex hormones in both men and women. In women, follicle-stimulating hormone stimulates the development and maturation of the follicles and ova. As the follicle develops it produces oestrogen in increasing amounts which at mid-cycle stimulates the release of LH. This causes rupture of the follicle with ovulation and converts the follicle into the corpus luteum which secretes progesterone. In men, luteinising hormone stimulates the interstitial cells of the testis to secrete testosterone, which in turn has a direct effect on the seminiferous tubules.

Gonadotrophic substances with luteinising or follicle-stimulating activity or both are used in the treatment of infertility (p. 2253.1), chiefly in females but also in males. Such substances include chorionic gonadotrophin (p. 2258.1) which possesses LH activity and human menopausal gonadotrophins (p. 2284.2) which possess both LH and FSH activity.

Lutropin alfa is a recombinant human luteinising hormone used to induce ovulation in women with severe deficiency of luteinising and follicle-stimulating hormones. It is used at the same time as a preparation with follicle-stimulating activity, usually follitropin alfa. The dosage and schedule of treatment must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles or both. Treatment is usually begun with 75 units of lutropin alfa daily by subcutaneous injection for 7 to 14 days, accompanied by FSH. If there is no response, the FSH dosage may be increased at 7- or 14-day intervals until an adequate but not excessive response is achieved. A treatment cycle of up to 5 weeks may be needed. Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units to induce ovulation. These patients are generally amenorrhoeic and treatment may be started at any time.

References.

1. The European Recombinant Human LH Study Group. Recombinant human luteinizing hormone (LH) to support recombinant human follicle-stimulating hormone (FSH)-induced follicular development in LH- and FSH-deficient anovulatory women: a dose-finding study. *J Clin Endocrinol Metab* 1998; 83: 1507–14.
2. Burgués S, The Spanish Collaborative Group on Female Hypogonadotrophic Hypogonadism. The effectiveness and safety of recombinant human LH to support follicular development induced by recombinant human FSH in WHO group 1 anovulation: evidence from a multicentre study in Spain. *Hum Reprod* 2001; 16: 2525–32.
3. The European Recombinant LH Study Group. Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study. *J Clin Endocrinol Metab* 2001; 86: 2607–18.
4. Dhillon S, Keating GM. Lutropin alfa. *Drugs* 2008; 68: 1529–40.

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p. 2284.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lutropin alfa 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 07/10/11)

Pharmacokinetics

The absolute bioavailability of lutropin alfa after subcutaneous doses is about 60%, and the terminal half-life is at least 10 to 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Luveris; *Austral.*: Luveris; *Austria*: Luveris; *Belg.*: Luveris; *Braz.*: Luveris; *Canad.*: Luveris; *Chile*: Luveris; *China*: Luveris (乐芮); *Cz.*: Luveris; *Denm.*: Luveris; *Fin.*: Luveris; *Fr.*: Luveris; *Ger.*: Luveris; *Gr.*: Luveris; *Hong Kong*: Luveris; *Hung.*: Luveris; *India*: Luveris; *Indon.*: Luveris; *Irl.*: Luveris; *Israel*: Luveris; *Ital.*: Luveris; *Malaysia*: Luveris; *Mex.*: Luveris†; *Neth.*: Luveris; *Norw.*: Luveris; *NZ*: Luveris; *Philipp.*: Luveris; *Pol.*: Luveris; *Port.*: Luveris; *Rus.*: Luveris (Лувэрис); *S.Afr.*: Luveris; *Singapore*: Luveris; *Spain*: Luveris; *Swed.*: Luveris; *Switz.*: Luveris; *Thai.*: Luveris; *Turk.*: Luveris; *UK*: Luveris; *USA*: Luveris†; *Venez.*: Luveris.

Multi-ingredient Preparations. *Arg.*: Pergoveris; *Austria*: Pergoveris; *Belg.*: Pergoveris; *Braz.*: Pergoveris; *Cz.*: Pergoveris; *Denm.*: Pergoveris; *Fr.*: Pergoveris; *Ger.*: Pergoveris; *Gr.*: Pergoveris; *Hung.*: Pergoveris; *Irl.*: Pergoveris; *Israel*: Pergoveris; *Ital.*: Pergoveris; *Neth.*: Pergoveris; *Norw.*: Pergoveris; *Pol.*: Pergoveris; *Port.*: Pergoveris; *Rus.*: HuMoG (ХуМоГ); *Singapore*: Pergoveris; *Spain*: Pergoveris; *Swed.*: Pergoveris†; *Switz.*: Pergoveris; *UK*: Pergoveris.

Lynestrenol (BAN, USAN, rINN)

Ethinylestrenol; Ethinylestrenolo; Linestrenol; Linestrenolis; Lineszrenol; Linoestrenol; Lynenol; Lynestrenol; Lynestrenolo; Lynestrenolum; Lynoestrenol; NSC-37725; Линестренол.

19-Nor-17α-pregn-4-en-20-yn-17β-ol.

$C_{20}H_{28}O$=284.4

CAS — 52-76-6.
ATC — G03AC02; G03DC03.
ATC Vet — QG03AC02; QG03DC03.
UNII — N2ZBALG4U5.

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

Ph. Eur. 8: (Lynestrenol). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol and in acetone. Protect from light.

Profile

Lynestrenol is a progestogen (see Progesterone, p. 2300.2) structurally related to norethisterone that is used alone or as the progestogenic component of oral contraceptives (see p. 2231.3). Typical oral daily doses for contraception are 500 micrograms when used as a progestogen-only preparation, and 0.75 or 2.5 mg when combined with an oestrogen. When used alone for menstrual disorders, doses of 5 to 10 mg daily are given, often as cyclical regimens.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lynestrenol 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 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Exluton; *Austria*: Orgametril; *Belg.*: Orgametril; *Braz.*: Exluton; *Chile*: Exluton; Linosun; Normalac; *Cz.*: Orgametril; *Denm.*: Orgametril†; *Fin.*: Orgametril; *Fr.*: Orgametril†; *Gr.*: Orgametril; *Hung.*: Orgametril†; *Indon.*: Endometril; Exluton; *Mex.*: Exluton; *Neth.*: Exluton; Orgametril; *Philipp.*: Amber; Daphne; Exluton; *Pol.*: Orgametril; *Rus.*: Exluton (Экслютон); Orgametril (Оргаметрил); *Spain*: Orgametril; *Swed.*: Exlutena; Orgametril; *Thai.*: Dailyton; Exluton; *Turk.*: Orgametril; *Ukr.*: Exluton (Экслютон); Orgametril (Оргаметрил); *Venez.*: Exluton; Normalac.

Multi-ingredient Preparations. *Braz.*: Ovoresta†; *Chile*: Anovulatorios; *Ger.*: Ovoresta M†; *Neth.*: Ministat; *Swed.*: Restovar; *Turk.*: Lyndiol.

Medrogestone (BAN, USAN, rINN)

AY-62022; Medrogeston; Medrogestona; Medrogestone; Medrogestoni; Medrogestonum; Metrogestone; NSC-123018; R-13-615; Медроестон.

6,17α-Dimethylpregna-4,6-diene-3,20-dione.

$C_{23}H_{32}O_2$=340.5

CAS — 977-79-7.
ATC — G03DB03.
ATC Vet — QG03DB03.
UNII — 077DN93G5B.

Profile

Medrogestone is a progestogen structurally related to progesterone (p. 2300.2) that is used in the treatment of menstrual disorders, and as the progestogen in menopausal HRT (see p. 2244.1). It is usually given orally in daily doses of 5 to 10 mg, generally in a cyclical regimen. Higher doses were used in the treatment of endometrial carcinoma, prostatic hyperplasia, and breast disorders including carcinoma. It has also been used for threatened or recurrent miscarriage, but such use is not recommended unless there is proven progesterone deficiency.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Colprone.

Multi-ingredient Preparations. *Ger.*: Presomen Compositum; Presomen conti; *S.Afr.*: Prempak N†.

Medroxyprogesterone Acetate

(BANM, rINNM)

Acetato de medroxiprogesterona; Medroksiprogesteron Asetat; Medroksiprogesteroniasetaatti; Medroksiprogesterono acetatas; Medroksyprogesteronu octan; Medroxiprogesterona, acetato de; Medroxiprogesteronacetat; Medroxiprogeszteron-acetát; Medroxyprogesteronacetat; Medroxyprogesteron-acetát; Médroxyprogestérone, Acétate de; Medroxyprogesteroni Acetas; Methylacetoxyprogesterone; Metipregnone; NSC-26386; Медроксипрогестерона Ацетат.

6α-Methyl-3,20-dioxopregn-4-en-17α-yl acetate; 17α-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate.

$C_{24}H_{34}O_4$=386.5

CAS — 520-85-4 (medroxyprogesterone); 71-58-9 (medroxyprogesterone acetate).

ATC — G03AC06; G03DA02; L02AB02.

ATC Vet — QG03AC06; QG03DA02; QL02AB02.

UNII — C2QI4IOI2G.

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

Ph. Eur. 8: (Medroxyprogesterone Acetate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 36: (Medroxyprogesterone Acetate). A white to off-white, odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone and in dioxan; freely soluble in chloroform; slightly soluble in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Medroxyprogesterone acetate is a progestogen structurally related to progesterone, with actions and uses similar to those of the progestogens in general (see Progesterone, p. 2300.2). It is given orally or, for prolonged action, as an aqueous suspension by intramuscular or subcutaneous injection, depending on the product.

It is used for the treatment of **menorrhagia** (p. 2300.3) and **secondary amenorrhoea** in oral doses of 2.5 to 10 mg daily for 5 to 10 days starting on the assumed or calculated 16th to 21st day of the menstrual cycle, although treatment may begin on any day in secondary amenorrhoea.

In the treatment of mild to moderate **endometriosis** (p. 2264.1) usual oral doses are 10 mg three times daily for 90 consecutive days, or 50 mg weekly or 100 mg every 2 weeks by intramuscular injection for at least 6 months. An alternative formulation used for the treatment of pain associated with endometriosis is given in a dose of 104 mg in 0.65 mL by subcutaneous injection once every 12 to 14 weeks.

Medroxyprogesterone acetate is also given by injection as a **contraceptive** (see under Hormonal Contraceptives, p. 2231.3). As a progestogen-only contraceptive an intramuscular dose of 150 mg is given every 12 or 13 weeks. A combined contraceptive injection containing medroxyprogesterone acetate 25 mg with estradiol cipionate 5 mg is given monthly as an intramuscular injection. An alternative formulation used as a progestogen-only contraceptive is given as a dose of medroxyprogesterone acetate 104 mg in 0.65 mL by subcutaneous injection once every 12 to 14 weeks.

When used as the progestogen component of **menopausal HRT** (see p. 2244.2), medroxyprogesterone acetate is given orally in a variety of regimens including 1.5, 2.5, or 5 mg daily continuously, 5 or 10 mg daily for 12 to 14 days of a 28-day cycle, and 20 mg daily for 14 days of a 91-day cycle.

Medroxyprogesterone acetate may also be used in the palliative treatment of some hormone-dependent malignant neoplasms. In **breast carcinoma** (see below) oral doses of 0.4 to 1.5 g daily may be given, although doses up to 2 g daily have been used in the past. Intramuscular medroxyprogesterone acetate has been given in initial doses of 500 mg daily for 4 weeks, then in maintenance doses twice weekly. In **endometrial** (below) and **renal carcinoma** (p. 708.3) oral doses have ranged from 200 to 600 mg daily. Initial doses of 0.6 to 1.2 g weekly have been given by intramuscular injection, reducing to a maintenance schedule of as little as 450 mg monthly. In **prostatic carcinoma** (p. 712.3) oral doses have been 100 to 600 mg daily; 500 mg has also been given by intramuscular injection, initially twice weekly for 3 months then once weekly for maintenance.

Cachexia. Medroxyprogesterone may improve appetite and food intake, and prevent loss of body-weight in cachexia (p. 2289.3) associated with severe chronic disorders,[1-3] although information is limited.

1. Simons JPFHA, *et al.*: Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. *J Clin Oncol* 1996; **14:** 1077–84.
2. Simons JPFHA, *et al.* Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, nonhormone-sensitive cancer: a randomized, placebo-controlled trial. *Cancer* 1998; **82:** 553–60.
3. Madeddu C, *et al.* Medroxyprogesterone acetate in the management of cancer cachexia. *Expert Opin Pharmacother* 2009; **10:** 1359–66.

Contraception. Medroxyprogesterone acetate has an established use as a parenteral progestogen-only contraceptive (p. 2232.3). It has also been developed as the progestogenic component of a combined injectable contraceptive and has been investigated as a component of hormonal contraceptives for men.

References.

1. Garza-Flores J, *et al.* Introduction of Cyclofem once-a-month injectable contraceptive in Mexico. *Contraception* 1998; **58:** 7–12.
2. Kaunitz AM, *et al.* Comparative safety, efficacy, and cycle control of Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) and Ortho-Novum 7/7/7 oral contraceptive (norethindrone/ethinyl estradiol triphasic). *Contraception* 1999; **60:** 179–87.
3. Kaunitz AM. Current concepts regarding use of DMPA. *J Reprod Med* 2002; **47** (suppl): 785–9.
4. Turner L, *et al.* Contraceptive efficacy of a depot progestin and androgen combination in men. *J Clin Endocrinol Metab* 2003; **88:** 4659–67.
5. Gu YQ, *et al.* Male hormonal contraception: effects of injections of testosterone undecanoate and depot medroxyprogesterone acetate at eight-week intervals in Chinese men. *J Clin Endocrinol Metab* 2004; **89:** 2254–62.
6. Page ST, *et al.* Testosterone gel combined with depomedroxyprogesterone acetate is an effective male hormonal contraceptive regimen and is not enhanced by the addition of a GnRH antagonist. *J Clin Endocrinol Metab* 2006; **91:** 4374–80.

Epilepsy. Early findings[1] suggested that medroxyprogesterone acetate might be of value in the management of catamenial epilepsy (p. 506.1). In a later review[2] it was suggested that hormonal manipulation with drugs such as medroxyprogesterone should be reserved for highly selected groups under close supervision.

1. Mattson RH, *et al.* Treatment of seizures with medroxyprogesterone acetate: preliminary report. *Neurology* 1984; **34:** 1255–8.
2. Herkes GK. Drug treatment of catamenial epilepsy. *CNS Drugs* 1995; **3:** 260–6.

Male hypersexuality. The anti-androgenic action of medroxyprogesterone has been used for suppression of libido in the control of men with deviant or disinhibited sexual behaviour[1-8] (see Disturbed Behaviour, p. 1030.2). Most have received intramuscular medroxyprogesterone acetate; doses of about 300 mg weekly have been used,[3] but ranged from 100 mg each month to 500 mg each week in one report of 5 cases,[6] and up to 750 mg each week in another case.[6] Oral treatment with 30 mg daily was also successful in 1 case.[5]

1. Kiersch TA. Treatment of sex offenders with Depo-Provera. *Bull Am Acad Psychiatry Law* 1990; **18:** 179–87.
2. Weiner MF, *et al.* Intramuscular medroxyprogesterone acetate for sexual aggression in elderly men. *Lancet* 1992; **339:** 1121–2.
3. Kravitz HM, *et al.* Medroxyprogesterone treatment for paraphiliacs. *Bull Am Acad Psychiatry Law* 1995; **23:** 19–33.
4. Britton KR. Medroxyprogesterone in the treatment of aggressive hypersexual behaviour in traumatic brain injury. *Brain Inj* 1998; **12:** 703–7.
5. Brooks JO, Walkar MV. Inappropriate masturbation and schizophrenia. *J Clin Psychiatry* 2000; **61:** 451.
6. Stewart JT. Optimizing antilibidinal treatment with medroxyprogesterone acetate. *J Am Geriatr Soc* 2005; **53:** 359–60.
7. Maletzky BM, *et al.* The Oregon depo-Provera program: a five-year follow-up. *Sex Abuse* 2006; **18:** 303–16.
8. Light SA, Holroyd S. The use of medroxyprogesterone acetate for the treatment of sexually inappropriate behaviour in patients with dementia. *J Psychiatry Neurosci* 2006; **31:** 132–4.

Malignant neoplasms. *BREAST.* Progestogens are used as second- or third-choice drugs in the hormonal therapy of advanced breast cancer (p. 702.1). Some references to the use of medroxyprogesterone acetate in advanced breast cancer are cited below.[1-8] Comparative studies have shown that patients respond equally well to medroxyprogesterone and either mepitiostane,[1] aminoglutethimide,[2] or oophorectomy.[3]

1. Izuo M, *et al.* A phase III trial of oral high-dose medroxyprogesterone acetate (MPA) versus mepitiostane in advanced postmenopausal breast cancer. *Cancer* 1985; **56:** 2576–9.
2. Canney PA, *et al.* Randomized trial comparing aminoglutethimide with high-dose medroxyprogesterone acetate in therapy for advanced breast carcinoma. *J Natl Cancer Inst* 1988; **80:** 1147–51.
3. Martoni A, *et al.* High-dose medroxyprogesterone acetate versus oophorectomy as first-line therapy of advanced breast cancer in premenopausal patients. *Oncology* 1991; **48:** 1–6.
4. Muss HB, *et al.* Tamoxifen versus high-dose oral medroxyprogesterone acetate as initial endocrine therapy for patients with metastatic breast cancer: a Piedmont Oncology Association study. *J Clin Oncol* 1994; **12:** 1630–8.
5. Clinton OP, *et al.* A prospective randomized trial to evaluate different oral dose regimens of medroxyprogesterone acetate in women with advanced breast cancer. *Clin Oncol* 1995; **7:** 251–6.
6. Byrne MJ, *et al.* Medroxyprogesterone acetate addition or substitution for tamoxifen in advanced tamoxifen-resistant breast cancer: a phase III randomized trial. *J Clin Oncol* 1997; **15:** 3141–8.
7. Koyama H, *et al.* A randomized controlled comparative study of oral medroxyprogesterone acetate 1,200 and 600 mg in patients with advanced or recurrent breast cancer. *Oncology* 1999; **56:** 283–90.
8. Kloke O, *et al.* Maintenance treatment with medroxyprogesterone acetate in patients with advanced breast cancer responding to chemotherapy: results of a randomized trial. *Breast Cancer Res Treat* 1999; **55:** 51–9.

ENDOMETRIUM. Progestogens are used in the treatment of advanced endometrial carcinoma (p. 704.3) but there are doubts about their value in the earlier stages of disease.[1] Medroxyprogesterone acetate was effective in a rare case of low-grade endometrial stromal sarcoma.[2] It has also been used in a few patients as adjuvant therapy after surgery[3] and for the treatment of metastatic disease.[4]

1. Martin-Hirsch PL, *et al.* Progestagens for endometrial cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 27/06/08).
2. Rand RJ, Lowe JW. Low-grade endometrial stromal sarcoma treated with a progestogen. *Br J Hosp Med* 1990; **43:** 154–6.
3. Amant F, *et al.* Clinical study investigating the role of lymphadenectomy, surgical castration and adjuvant hormonal treatment in endometrial stromal sarcoma. *Br J Cancer* 2007; **97:** 1194–9.
4. Pink D, *et al.* Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. *Gynecol Oncol* 2006; **101:** 464–9.

Respiratory disorders. Reviews of the use of medroxyprogesterone acetate in obstructive sleep apnoea have concluded that it has a limited role.[1,2]

Progesterone and, more commonly, medroxyprogesterone acetate are used in the treatment of pulmonary lymphangioleiomyomatosis, a rare disease affecting only women.[3-7] Anecdotal evidence suggests some patients improve or stabilise on treatment, possibly those with chylous effusions or chylous ascites.[8] However, a more rapid decline in lung function has also been seen with progestogen therapy in some groups.[5,6]

Medroxyprogesterone acetate was reported to be effective in treating congenital central hypoventilation syndrome in 2 children.[9] It has also been used in adults with central hypoventilation resulting from brainstem stroke[10] and other causes.[11] Medroxyprogesterone has also been investigated for its effects on respiration in chronic obstructive pulmonary disease, sometimes with acetazolamide.[12-14]

1. Millman RP. Medroxyprogesterone and obstructive sleep apnea. *Chest* 1989; **96:** 225–6.
2. Terra SG, Oberg KC. Medroxyprogesterone acetate in the treatment of obstructive sleep apnea. *Ann Pharmacother* 1997; **31:** 776–8.
3. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999; **54:** 254–64.
4. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000; **55:** 1052–7.
5. Johnson SR, *et al.* Survival and disease progression in UK patients with lymphangioleiomyomatosis. *Thorax* 2004; **59:** 800–3.
6. Taveira-DaSilva AM, *et al.* Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. *Chest* 2004; **126:** 1867–74.
7. Schiavina M, *et al.* Efficacy of hormonal manipulation in lymphangioleiomyomatosis: a 20-year-experience in 36 patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2007; **24:** 39–50.
8. Taylor JR, *et al.* Lymphangioleiomyomatosis: clinical course in 32 patients. *N Engl J Med* 1990; **323:** 1254–60.
9. Millerad J, *et al.* Alveolar hypoventilation treated with medroxyprogesterone. *Arch Dis Child* 1985; **60:** 150–5.
10. Smyth A, Riley M. Chronic respiratory failure: an unusual cause and treatment. *Thorax* 2002; **57:** 835–6.
11. Bootsma GP, *et al.* Chronic respiratory failure. *Thorax* 2003; **58:** 281.
12. Wagenaar M, *et al.* Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; **20:** 1130–7.
13. Wagenaar M, *et al.* Comparison of acetazolamide and medroxyprogesterone as respiratory stimulants in hypercapnic patients with COPD. *Chest* 2003; **123:** 1450–9.
14. Saaresranta T, *et al.* Medroxyprogesterone improves nocturnal breathing in postmenopausal women with chronic obstructive pulmonary disease. *Respir Res* 2005; **6:** 28.

Sickle-cell disease. The frequency of painful crises has been reduced in women with homozygous sickle-cell disease (p. 1123.2) given intramuscular depot medroxyprogesterone acetate,[1,2] and it is now considered to be a suitable contraceptive for this group (see also Sickle-cell Disease, under Precautions of Hormonal Contraceptives, p. 2242.1).

1. de Ceulaer K, *et al.* Medroxyprogesterone acetate and homozygous sickle-cell disease. *Lancet* 1982; **ii:** 229–31.
2. de Abood M, *et al.* Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. *Contraception* 1997; **56:** 313–16.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3. Medroxyprogesterone acetate may have glucocorticoid effects when given long term at high doses.

Breast feeding. Medroxyprogesterone is reported to be distributed into breast milk when given as a depot progestogen-only contraceptive.[1] No adverse effects have been seen in breast-fed infants of mothers given medroxyprogesterone, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding. It is recommended that progestogen-only parenteral contraceptives should not be used until 6 weeks after birth if the woman is breast feeding (see Breast Feeding under Hormonal Contraceptives, p. 2241.1) but the evidence for delaying postpartum use

of medroxyprogesterone in this group has been questioned.[3]

1. Schwallie PC. The effect of depot-medroxyprogesterone acetate on the fetus and nursing infant: a review. *Contraception* 1981; 23: 375–86.
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 27/06/08)
3. Rodriguez MI, Kaunitz AM. An evidence-based approach to postpartum use of depot medroxyprogesterone acetate in breastfeeding women. *Contraception* 2009; 80: 4–6.

Carcinogenicity. The risk of various cancers associated with the use of depot medroxyprogesterone acetate as a contraceptive has been evaluated by WHO.[1] Overall, there was no increase in risk of breast cancer, although there is some evidence that current or recent use may be associated with a slight increase in risk (see also p. 2234.2). There was no significant increased risk of cervical cancer (see also p. 2235.1), and a protective effect against endometrial cancer (see p. 2235.2). In contrast to combined oral contraceptives, there was no evidence of a protective effect against ovarian cancer (p. 2236.1).

1. Anonymous. Depot-medroxyprogesterone acetate (DMPA) and cancer: memorandum from a WHO meeting. *Bull WHO* 1993; 71: 669–76.

Effects on bone density. Use of medroxyprogesterone acetate as a parenteral progestogen-only contraceptive has been associated with reductions in bone density (see under Effects on the Musculoskeletal System, p. 2239.3). This effect has also been reported after oral doses for menstrual disorders,[1] and is thought to be due to medroxyprogesterone-induced oestrogen deficiency.

1. Cundy T, *et al.* Short-term effects of high dose oral medroxyprogesterone acetate on bone density in premenopausal women. *J Clin Endocrinol Metab* 1996; 81: 1014–17.

Effects on the skin. Acute local skin necrosis has been reported[1] after the intramuscular injection of medroxyprogesterone acetate as a depot contraceptive. A case of pigmented purpura on the lower legs, occurring about 4 months after starting medroxyprogesterone acetate injections, has been described.[2]

1. Clark SM, Lanigan SW. Acute necrotic skin reaction to intramuscular Depo-Provera. *Br J Dermatol* 2000; 143: 1356–7.
2. Tsao H, Lerner LH. Pigmented purpuric eruption associated with injection medroxyprogesterone acetate. *J Am Acad Dermatol* 2000; 43: 308–10.

Glucocorticoid effects. There have been reports of Cushing's syndrome induced by medroxyprogesterone acetate in patients receiving long-term therapy with high doses for the treatment of malignant neoplasms[1-5] or paraphilia.[6] Cushingoid symptoms regressed when treatment was stopped. Medroxyprogesterone possesses glucocorticoid activity and there is a risk of adrenal insufficiency during periods of stress or after sudden withdrawal of treatment. Some[4] consider that patients should be monitored for glucose intolerance and adrenal insufficiency during treatment.

1. Siminoski K, *et al.* The Cushing syndrome induced by medroxyprogesterone acetate. *Ann Intern Med* 1989; 111: 758–60.
2. Donckier JE, *et al.* Cushing syndrome and medroxyprogesterone acetate. *Lancet* 1990; 335: 1094.
3. Grenfell A, *et al.* Cushing's syndrome and medroxyprogesterone acetate. *Lancet* 1990; 336: 256.
4. Merrin PK, Alexander WD. Cushing's syndrome induced by medroxyprogesterone. *BMJ* 1990; 301: 345.
5. Shotliff K, Nussey SS. Medroxyprogesterone acetate induced Cushing's syndrome. *Br J Clin Pharmacol* 1997; 44: 304.
6. Krueger RB, *et al.* Prescription of medroxyprogesterone acetate to a patient with pedophilia, resulting in Cushing's syndrome and adrenal insufficiency. *Sex Abuse* 2006; 18: 227–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies medroxyprogesterone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1] However, for a reference to the use of medroxyprogesterone acetate with buserelin acetate in the prevention of premenstrual exacerbations of porphyria in 2 women, see p. 2257.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). Aminoglutethimide markedly reduces plasma concentrations of medroxyprogesterone so that an increase in medroxyprogesterone dosage is likely to be required.

Pharmacokinetics

Medroxyprogesterone is absorbed from the gastrointestinal tract. In the blood, it is highly protein bound, principally to albumin. It is metabolised in the liver and excreted mainly as glucuronide conjugates in the urine and faeces. It has a half-life of about 16 to 30 hours after oral doses; the half-life may be as long as 50 days after intramuscular injection. Medroxyprogesterone is reported to be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Depo-Provera; Farlutale; Livomedrox; Map An†; Medrosterona; Veraplex; ***Austral.***: Depo-Provera; Depo-Ralovera; Medroxyhexal†; Provera; Ralovera; ***Austria***: Depocon; Farlutal; Prodafem; Sayana; ***Belg.***: Depo-Provera; Farlutal; Provera; Sayana; Veraplex; ***Braz.***: Acemedrox; Acetoflux; Contracep; Cycrin; Demedrox; Depo-Provera; Farlutal; Medroxitest; Medroxon; Provera; ***Canad.***: Apo-Medroxy; Depo-Provera; Gen-Medroxy†; Medroxy; Novo-Medrone†; Provera; ***Chile***: Depo-Prodasone; Farlutal†; Farlutes†; Prodasone; Provera†; ***China***: Bei En (倍恩); Depo Geston (迪波盖斯通); Depo-Provera (狄波-普维拉); Farlutal (法禄达); Mei Qu Luo (美曲罗); Provera (普维拉); ***Cz.***: Depo-Provera; Femihexal†; Medroplex; Provera; Sayana; ***Denm.***: Depo-Provera; Perlutex†; Provera; ***Fin.***: Depo-Provera; Farlutal; Mepastat†; Provera; ***Fr.***: Depo-Prodasone; Depo-Provera; Farlutal; ***Ger.***: Depo-Clinovir; MPA Gyn†; MPA-beta; MPA†; Sayana; ***Gr.***: Depo-Provera; Farlutal; Neolut; Progevera; Provera; ***Hong Kong***: Apo-Medroxy; Depo-Provera; Farlutal†; Provera; ***Hung.***: Depo-Provera; Provera; ***India***: Depo Progestin; Depo-Provera; Depro; Deviry; Dubloc; Empeea; Farlutal; Geeva; Maxogest; Medrigest; Medronorm; Medtet; Megest; Meprate; Modus; Orgamed; ***Indon.***: Planibu; Prothyra†; Provera; Triclofem†; Veraplex; ***Irl.***: Depo-Provera; Provera; Sayana; ***Israel***: Depo-Provera; Provera; Sayana; ***Ital.***: Depo-Provera; Farlutal; Provera; ***Jpn***: Hysron; ***Malaysia***: Condep; Depo-Provera; Non-Preg; Provera; Ravimed; Veraplex; ***Mex.***: Ciclotal†; Megestron; Provera; ***Neth.***: Depo-Provera; Megestron; Provera; Sayana; ***Norw.***: Depo-Provera; Farlutal†; Perlutex†; Provera; ***NZ***: Depo-Provera; Provera; ***Philipp.***: Depo-Provera; Deporeva; Depotrust; Lyndavel; Provera; Provestin; ***Pol.***: Depo-Provera; Gestomikron; Provera; Sayana; ***Port.***: Depo-Provera; Provera; ***Rus.***: Ciclotal (Циклотал); Depo-Provera (Депо-провера); Provera (Провера); Veraplex (Вераплекс); ***S.Afr.***: Depo-Provera; Hexal-MPA; Petogen; Provera; ***Singapore***: Depo-Provera; Provera; ***Spain***: Depo-Progevera; Farlutal; Progevera 250; Progevera; ***Swed.***: Depo-Provera; Gestapuran†; Provera; ***Switz.***: Depo-Provera; Farlutal; Prodafem; Sayana; ***Thai.***: Contracep; Depo-Gestin; Depo-M; Depo-Progesno; Depo-Progesta; Enaf; Farlutal; Manodepo; Medeton; Pheno-M†; Provera; Veraplex; ***Turk.***: Depo-Provera; Farlutal; ***UK***: Climanor; Depo-Provera; Provera; Sayana; ***Ukr.***: Depo-Provera (Депо-Провера); ***USA***: Depo-Provera; Depo-subQ Provera; Provera; ***Venez.***: Depo-Provera; Provera.

Multi-ingredient Preparations. ***Arg.***: Cyclofem; Farludiol Ciclo; Farludiol; ***Austral.***: Premia Continuous; Premia†; ***Belg.***: Diviplus; Diviva; ***Braz.***: Cyclofemina; Dilena; Premelle Ciclo; Premelle; Prempro Bifasico; Prempro Monofasico; Repogen Ciclo; Repogen Conti; Selecta; ***Canad.***: Premplus; ***Chile***: Climatrol Continuo†; Climatrol HT Continuo; Climatrol HT†; Conpremin Pak Plus†; Conpremin Pak†; Enadiol CC†; Enadiol MP†; Estranova 30 Simple†; Estranova CC†; Farlupost†; Kilios; Novafac 30; Novafac CC; Novafac†; Novafem; Primaquin MP Continuo†; Primaquin MP†; Profemina MP†; ***China***: Lunella (月纳); Premelle (倍美罗); ***Cz.***: Divina; Diviseq; Indivina; ***Denm.***: Divina Plus; Divina; Indivina; Trevina; ***Fin.***: Divina; Divitren; Indivina; ***Fr.***: Divina; Duova; Precyclan†; ***Ger.***: Climopax Cyclo; Climopax; Gianda†; Indivina; Osmil†; Sisare 28†; Sisare†; ***Gr.***: Divina; Estopause; Premelle Cycle; Premelle; ***Hong Kong***: Cyclofem; Dilena†; Premelle Cycle†; Premelle; ***Hung.***: Divina; Indivina; ***Indon.***: Cyclofem†; ***Irl.***: Indivina; Premique Cycle; Premique; ***Ital.***: Filena; Premelle Combinato†; Premia; ***Malaysia***: Premelle; ***Mex.***: Cyclofemina; Dilena; Premelle; Xofemina; ***Norw.***: Indivina; ***NZ***: Premia Continuous; ***Philipp.***: Premelle Cycle; Premelle; ***Pol.***: Divina; Diviseq; Indivina; ***Port.***: Dilena; ***Rus.***: Divina (Дивина); Diviseq (Дивисек); Divitren (Дивитрен)†; Indivina (Индивина); ***S.Afr.***: Divina†; Premelle Cycle; Premelle; Trivina†; ***Singapore***: Premelle Cycle; Premelle; ***Spain***: Medrivas Antib; Medrivas; Perifem; ***Swed.***: Divina Plus; Indivina; Trivina; ***Switz.***: Diviseq†; Indivina; Triaval†; ***Thai.***: Diviseq†; Indivina†; ***Turk.***: Divina; Premelle Cycle; Premelle†; ***UK***: Indivina; Premique Cycle†; Premique; Tridestra; ***Ukr.***: Divina (Дивина)†; Indivina (Индивина)†; ***USA***: Premphase; Prempro; ***Venez.***: Climatrol HT Ciclico; Climatrol HT Continuo; Premelle Continuo.

Pharmacopoeial Preparations

BP 2014: Medroxyprogesterone Injection; Medroxyprogesterone Tablets;

USP 36: Medroxyprogesterone Acetate Injectable Suspension; Medroxyprogesterone Acetate Tablets.

Megestrol Acetate *(BANM, USAN, rINNM)*

Acetato de megestrol; BDH-1298; Compound 5071; Megestol Asetat; Mégestrol, Acétate de; Megestrol, acetato de; Megestrolacetat; Megestrol-acetát; Megestroli Acetas; Megestroliasetaatti; Megestrolio acetatas; Megesztrol-acetát; NSC-71423; SC-10363; Мегестрола Ацетат.

6-Methyl-3,20-dioxopregna-4,6-dien-17α-yl acetate; 17α-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate.

$C_{24}H_{32}O_4$=384.5

CAS — 3562-63-8 (megestrol); 595-33-5 (megestrol acetate).

ATC — G03AC05; G03DB02; L02AB01.

ATC Vet — QG03AC05; QG03DB02; QL02AB01.

UNII — TJ2M0FR8ES.

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

Ph. Eur. 8: (Megestrol Acetate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone. Protect from light.

USP 36: (Megestrol Acetate). A white to creamy-white, essentially odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol; soluble in acetone; very soluble in chloroform; slightly soluble in ether and in fixed oils. Protect from light.

Uses and Administration

Megestrol acetate is a progestogen structurally related to progesterone (p. 2300.2).

It is used for the palliative treatment of some hormone-dependent malignant neoplasms (see p. 2290.1). Oral doses of 40 to 320 mg daily in divided doses may be given in **endometrial carcinoma**, and doses of 40 mg four times daily or 160 mg once daily may be used in **breast cancer.**

Megestrol acetate is also used in the treatment of **anorexia and cachexia** (see below) in patients with cancer or AIDS. The usual dose is 400 to 800 mg daily, as tablets or oral suspension. A suspension of megestrol acetate that has an increased bioavailability is also available (*Megace ES; Par Pharmaceutical, USA*) and is given in a dose of 625 mg in 5 mL daily for anorexia, cachexia, or unexplained significant weight loss in patients with AIDS.

Cachexia. In some patients with severe chronic disorders or malignant neoplasms, anorexia (loss of appetite) forms part of a syndrome of metabolic abnormalities and progressive physical wasting known as cachexia. Improved nutrition and dietary counselling are usually insufficient to reverse cachexia, and drug therapy has been tried to stimulate appetite and promote weight gain.

In **cancer-related cachexia**, corticosteroids are frequently used for appetite stimulation in patients with advanced malignancies, although they do not appear to promote weight gain. However, because their effect is usually temporary, and adverse effects occur with prolonged use,[1-3] they tend to be reserved for short-term treatment in patients with a limited life expectancy of weeks.[4] Megestrol has produced weight gain in some randomised controlled studies,[5] although some of this may result from increase in fat mass rather than increase in lean body-mass.[2,3] It is generally used in patients with a longer life expectancy of months.[4] Similar properties have been reported with medroxyprogesterone.[1] A systematic review[6] concluded that only corticosteroids and the progestogens megestrol and medroxyprogesterone had sufficient evidence to support their use in cancer-related anorexia. Anabolic steroids have also been tried, but further evaluation is necessary;[1,7] a comparison of megestrol or dexamethasone with fluoxymesterone found the latter to be less effective than the progestogen or the corticosteroid.[8] Prokinetic drugs such as metoclopramide may be useful in patients whose symptoms are secondary to decreased gastrointestinal motility,[1,2] although relief of nausea may not necessarily lead to improved caloric intake or appetite.[6] It has been suggested that NSAIDs might inhibit the effects of pro-inflammatory cytokines associated with weight loss in cancer patients. The addition of ibuprofen improved the response to megestrol in one small study,[9] but more work is needed. There has also been interest in the effects of eicosapentaenoic acid, which may inhibit muscle protein degradation, but study results have been mixed[3] and a systematic review[10] concluded that there was insufficient evidence to recommend the use of eicosapentaenoic acid. Further investigation is needed to confirm its clinical effects, possibly using higher doses or treating for longer periods than have been so far reported.[6] Thalidomide was found to attenuate weight loss in a study[11] of patients with advanced pancreatic cancer, but quality of life and duration of survival were not significantly improved. Combination anticachectic therapy has also been investigated. A study comparing an oral progestogen (medroxyprogesterone or megestrol), eicosapentaenoic acid, carnitine, thalidomide, or a combination of all 4, in patients with cancer cachexia, found that the individual treatments were ineffective or at best mildly effective, but that the combined treatment produced significant benefit.[12] Other drugs studied but with little, if any, benefit include cannabinoids, cyproheptadine and hydrazine.[1,2,6]

High-dose megestrol[13-15] or oxandrolone[16-19] are effective in **HIV-related cachexia**, a topic discussed under HIV-associated Wasting, p. 959.1.

Management of cachexia associated with **other chronic conditions**, including in dialysis patients[20] and the elderly,[21] is less well studied. There have been controversies about the relative risks and benefits, particularly in the latter group: increased mortality was reported in one study of the

use of megestrol to treat significant weight loss in the elderly,[22] although others have reported benefit.[23]

Other compounds under investigation in cachectic states include growth hormone[19] and the endogenous hormones ghrelin[24] and melatonin,[7] and selective androgen receptor modulators.

1. Mantovani G, *et al.* Managing cancer-related anorexia/cachexia. *Drugs* 2001; 61: 499–514.
2. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. *CA Cancer J Clin* 2002; 52: 72–91.
3. Tisdale MJ. Clinical anticachexia treatments. *Nutr Clin Pract* 2006; 21: 168–74.
4. Jatoi A. Pharmacologic therapy for the cancer anorexia/weight loss syndrome: a data-driven, practical approach. *J Support Oncol* 2006; 4: 499–502.
5. Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia-cachexia syndrome. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2005 (accessed 27/06/08).
6. Yavuzsen T, *et al.* Systematic review of the treatment of cancer-associated anorexia and weight loss. *J Clin Oncol* 2005; 23: 8500–11.
7. Bossola M, *et al.* Cancer cachexia: it's time for more clinical trials. *Ann Surg Oncol* 2007; 14: 276–85.
8. Loprinzi CL, *et al.* Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol* 1999; 17: 3299–3306.
9. McMillan DC, *et al.* A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. *Br J Cancer* 1999; 79: 495–500.
10. Dewey A, *et al.* Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2007 (accessed 27/06/08).
11. Gordon JN, *et al.* Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005; 54: 540–5.
12. Mantovani G, *et al.* Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist* 2010; 15: 200–11.
13. Von Roenn JH, *et al.* Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med* 1994; 121: 393–9.
14. Oster MH, *et al.* Megestrol acetate in patients with AIDS and cachexia. *Ann Intern Med* 1994; 121: 400–408.
15. Clarick RH, *et al.* Megestrol acetate treatment of growth failure in children infected with human immunodeficiency virus. *Pediatrics* 1997; 99: 354–7.
16. Strawford A, *et al.* Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial. *JAMA* 1999; 281: 1282–90.
17. Mwamburi DM, *et al.* Comparing megestrol acetate therapy with oxandrolone therapy for HIV-related weight loss: similar results in 2 months. *Clin Infect Dis* 2004; 38: 895–902.
18. Grunfeld C, *et al.* Oxandrolone in the treatment of HIV-associated weight loss in men: a randomized, double-blind, placebo-controlled study. *J Acquir Immune Defic Syndr* 2006; 41: 304–14.
19. Guillet NP, *et al.* Update on clinical trials of growth factors and anabolic steroids in cachexia and wasting. *Am J Clin Nutr* 2010; 91 (suppl): 1143S–1147S.
20. Bossola M, *et al.* Mechanisms and treatment of anorexia in end-stage renal disease patients on hemodialysis. *J Ren Nutr* 2009; 19: 2–9.
21. Yeh S-S, *et al.* Pharmacological treatment of geriatric cachexia: evidence and safety in perspective. *J Am Med Dir Assoc* 2007; 8: 363–77.
22. Bodenner D, *et al.* A retrospective study of the association between megestrol acetate administration and mortality among nursing home residents with clinically significant weight loss. *Am J Geriatr Pharmacother* 2007; 5: 137–46.
23. Yeh S-S, *et al.* Usage of megestrol acetate in the treatment of anorexia-cachexia syndrome in the elderly. *J Nutr Health Aging* 2009; 13: 448–54.
24. Ashitani J, *et al.* Ghrelin and its therapeutic potential for cachectic patients. *Peptides* 2009; 30: 1951–6.

Hot flushes. Megestrol has been used to treat hot flushes in women with breast cancer (to avoid the potentially tumour-stimulating effects of an oestrogen—see Malignant Neoplasms, under Precautions of HRT, p. 2250.2), as well as in men with hot flushes after orchidectomy or anti-androgen therapy for prostate cancer.[1] Therapy, which involved low oral doses of 20 mg twice daily, was associated with a decrease in frequency of flushes of 50% or more in about three-quarters of all patients. About 3 years after the study had finished, these patients were asked about any ongoing use of megestrol and the occurrence of hot flushes.[2] Although symptoms still occurred in many of the patients taking megestrol, they were less common and less severe than in those who had stopped therapy, which included some who had stopped because of no perceived benefit. In patients taking megestrol, most were on doses of 20 mg or less daily. Information collected about adverse effects of megestrol revealed unexpected reports of chills, but these were described as being not as disabling as the hot flushes had been. A later study[3] in women with breast cancer found that a lower dose of 20 mg of megestrol acetate daily was as effective as 40 mg daily.

1. Loprinzi CL, *et al.* Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994; 331: 347–52.
2. Quella SK, *et al.* Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. *Cancer* 1998; 82: 1784–8.
3. Goodwin JW, *et al.* Phase III randomized placebo-controlled trial of two doses of megestrol acetate as treatment for menopausal symptoms in women with breast cancer: Southwest Oncology Group Study 9626. *J Clin Oncol* 2008; 26: 1650–6.

Malignant neoplasms. Like some other progestogens megestrol acetate is used in endometrial cancer (p. 704.3), and it has been reported to have similar efficacy to anastrozole[1] and tamoxifen[2] in postmenopausal women with advanced breast cancer (p. 702.1). There was no advantage in terms of response or survival in escalating the standard dose of megestrol (160 mg daily) to 800 or 1600 mg daily in a randomised study in women with breast cancer.[3]

1. Buzdar A, *et al.* Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. *J Clin Oncol* 1996; 14: 2000–11.
2. Stuart NSA, *et al.* A randomised phase III cross-over study of tamoxifen versus megestrol acetate in advanced and recurrent breast cancer. *Eur J Cancer* 1996; 32A: 1888–92.
3. Abrams J, *et al.* Dose-response trial of megestrol acetate in advanced breast cancer: cancer and Leukemia Group B phase III study 8741. *J Clin Oncol* 1999; 17: 64–73.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). The weight gain that may occur with megestrol acetate appears to be associated with an increased appetite and food intake rather than with fluid retention. Megestrol acetate may have glucocorticoid effects when given long term.

Effects on carbohydrate metabolism. Megestrol therapy has been associated with hyperglycaemia[1-3] or diabetes mellitus[4] in AIDS patients being treated for cachexia. It has been suggested that megestrol produces peripheral insulin resistance due to a glucocorticoid action.[5]

1. Panwalker AP. Hyperglycemia induced by megestrol acetate. *Ann Intern Med* 1992; 116: 878.
2. Bornemann M, Johnson AC. Endocrine effects of HIV infection. *N Engl J Med* 1993; 328: 890.
3. Kilby JM, Tabereaux PB. Severe hyperglycemia in an HIV clinic: preexisting versus drug-associated diabetes mellitus. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; 17: 46–50.
4. Henry K, *et al.* Diabetes mellitus induced by megestrol acetate in a patient with AIDS and cachexia. *Ann Intern Med* 1992; 116: 53–4.
5. Leinung MC, *et al.* Induction of adrenal suppression by megestrol acetate in patients with AIDS. *Ann Intern Med* 1995; 122: 843–5.

Effects on the musculoskeletal system. Severe pain of the hands similar to carpal tunnel syndrome occurred in 4 women while taking megestrol acetate and melphalan;[1] megestrol appeared to be responsible.

Osteoporosis and vertebral compression fractures occurred in 2 postmenopausal women taking megestrol for anorexia.[2] In both cases there was evidence of adrenocortical insufficiency that recovered after megestrol therapy was stopped, suggesting that the glucocorticoid effect of megestrol may have contributed to the development of osteoporosis.

1. DiSaia PJ, Morrow CP. Unusual side effect of megestrol acetate. *Am J Obstet Gynecol* 1977; 129: 460–1.
2. Wermers RA, *et al.* Osteoporosis associated with megestrol acetate. *Mayo Clin Proc* 2004; 79: 1557–61.

Effects on the respiratory system. Hyperpnoea occurred in 2 patients given megestrol acetate 80 mg three times daily.[1]

1. Fessel WJ. Megestrol acetate and hyperpnea. *Ann Intern Med* 1989; 110: 1034–5.

Glucocorticoid effects. Megestrol has glucocorticoid-like properties that can cause adrenocortical suppression in a significant number of patients.[1-5] There are also reports of adrenal insufficiency severe enough to require corticosteroid replacement therapy, usually with hydrocortisone.[3,6-9]

1. Naing KK, *et al.* Megestrol acetate therapy and secondary adrenal suppression. *Cancer* 1999; 86: 1044–9.
2. Ron IG, *et al.* A low-dose adrenocorticotropin test reveals impaired adrenal function in cancer patients receiving megestrol acetate therapy. *Eur J Cancer* 2002; 38: 1490–4.
3. Orme LM, *et al.* Megestrol acetate in pediatric oncology patients may lead to severe, symptomatic adrenal suppression. *Cancer* 2003; 98: 397–405.
4. Chidakel AR, *et al.* High prevalence of adrenal suppression during acute illness in hospitalized patients receiving megestrol acetate. *J Endocrinol Invest* 2006; 29: 136–40.
5. Dev R, *et al.* Association between megestrol acetate treatment and symptomatic adrenal insufficiency with hypogonadism in male patients with cancer. *Cancer* 2007; 110: 1173–7.
6. Mann M, *et al.* Glucocorticoidlike activity of megestrol: a summary of Food and Drug Administration experience and a review of the literature. *Arch Intern Med* 1997; 157: 1651–6.
7. Stockheim JA, *et al.* Adrenal suppression in children with the human immunodeficiency virus treated with megestrol acetate. *J Pediatr* 1999; 134: 368–70.
8. Bulchandani D, *et al.* Megestrol acetate-associated adrenal insufficiency. *Am J Geriatr Pharmacother* 2008; 6: 167–72.
9. Ibarra Barrueta O, *et al.* Insuficiencia suprarrenal asociada a acetato de megestrol en un paciente con el virus de la inmunodeficiencia humana. *Farm Hosp* 2009; 33: 115–16.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies megestrol 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 04/10/11)

Interactions

As for progestogens in general (see Progesterone, p. 2302.2).

Pharmacokinetics

Megestrol acetate is absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after an oral dose. Megestrol acetate is highly protein bound in plasma. It undergoes hepatic metabolism, with 57 to 78% of a dose being excreted in the urine and 8 to 30% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Megacorp; Meltonar†; Varigestrol; *Austral.*: Megace; *Belg.*: Megace; *Braz.*: Femigestrol; Gynodal; Megestat; *Canad.*: Megace; *Chile*: Megace; *China*: Ai Nuo Ke (艾诺克); AiKe (爱克); Jiadi (佳迪); Megace (梅格施); Mi Tuo Suo (米托索); Yi Li Zhi (宜利治); *Cz.*: Megace; Megaplex; *Denm.*: Megace; *Fin.*: Megace†; *Fr.*: Megace; *Ger.*: Megestat; *Gr.*: Megace; *Hong Kong*: Megace; *Hung.*: Megace; Megesin; Megyrina; *India*: Endace; *Indon.*: Megace†; Megaplex; *Irl.*: Megace; *Ital.*: Megace; Megestil; *Malaysia*: Megace; *Mex.*: Megace; Mestrel; *Neth.*: Megace†; *Norw.*: Megace; *NZ*: Megace; *Philipp.*: Megace†; Megaplex; *Pol.*: Cachexan†; Gestar†; Megace; Megalia; Megesin†; *Port.*: Acestrol; Megace; *Rus.*: Megace (Мегейс); Megaplex (Мегаплекс); *Spain*: Borea; Maygace; Megefren; *Swed.*: Megace; *Switz.*: Megestat†; *Thai.*: Megace; Megaplex; Mestrel; *Turk.*: Borea; Megace; *UK*: Megace; *USA*: Megace; *Venez.*: Megase.

Pharmacopoeial Preparations

BP 2014: Megestrol Tablets;

USP 36: Megestrol Acetate Oral Suspension; Megestrol Acetate Tablets.

Melengestrol Acetate *(BANM, USAN, rINNM)*

5373; Acetato de melengestrol; BDH-1921; Mélengestrol, Acétate de; Melengestroli Acetas; NSC-70968; Меленгестрола Ацетат.

17-Hydroxy-6-methyl-16-methylenepregna-4,6-diene-3,20-dione acetate.

$C_{25}H_{32}O_4$=396.5

CAS — 5633-18-1 (melengestrol); 2919-66-6 (melengestrol acetate).

UNII — 4W5HDS3936.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Melengestrol Acetate). A white to light yellow, crystalline powder. Insoluble in water; slightly soluble in alcohol; freely soluble in chloroform and in ethyl acetate. Store in airtight containers. Protect from light.

Profile

Melengestrol acetate is a progestogen that is used as an animal feed in beef heifers to improve feed efficiency, increase the rate of body-weight gain, and suppress oestrus.

WHO specifies an acceptable daily intake of melengestrol acetate as a residue in foods, and recommends maximum residue limits in various animal tissues.[1] However, it should be noted that, in the EU the use of melengestrol acetate and other steroidal hormones as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: sixty-sixth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 939* 2006. Also available at: http://libdoc.who.int/publications/2006/9241209399_eng.pdf (accessed 24/06/08)

Mepitiostane *(rINN)* ⊗

Mépitiostane; Mepitiostano; Mepitiostanum; S-10364; Мепитиостан.

17β-(1-Methoxycyclopentyloxy)-2α,3α-epithio-5α-androstane; Cyclopentanone 2α,3α-epithio-5α-androstan-17β-yl methyl acetal.

$C_{25}H_{40}O_2S$=404.7

CAS — 21362-69-6.

UNII — O00404969K.

Pharmacopoeias. In *Jpn.*

Profile

Mepitiostane has androgenic and anabolic properties (see Testosterone, p. 2305.1) and is given in usual oral doses of 10 mg twice daily for the management of neoplasms of the breast and anaemia associated with renal failure.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Thioderon.

Mesterolone (BAN, USAN, rINN) ⊗

Mesterolona; Mesterolonas; Mesterolonum; Mesterolone; Mesterolonil; Mésterolonum; Melzterolon; NSC-75054; SH-723; Mesteroponon.

17β-Hydroxy-1α-methyl-5α-androstan-3-one.

$C_{20}H_{32}O_2$=304.5

CAS — 1424-00-6.

ATC — G03BB01.

ATC Vet — QG03BB01.

UNII — 05R07SX99.

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

Ph. Eur. 8: (Mesterolone). A white or yellowish crystalline powder. Practically insoluble in water; sparingly soluble in acetone, in ethyl acetate, and in methyl alcohol.

Uses and Administration

Mesterolone has androgenic properties (see Testosterone, p. 2305.2) but is reported to have less inhibitory effect on intrinsic testicular function than testosterone.

Mesterolone is given orally in the treatment of androgen deficiency or male infertility associated with hypogonadism (p. 2252.3). Initial treatment with 75 to 100 mg daily, in 3 or 4 divided doses, is given for several months, followed by 50 to 75 mg daily for maintenance.

Adverse Effects and Precautions

As for androgens in general (see Testosterone, p. 2307.3).

Mesterolone is reported not to inhibit gonadotrophin secretion or spermatogenesis.

Pharmacokinetics

Mesterolone is rapidly and almost completely absorbed after an oral dose and peak serum concentrations occur after about 1.6 hours. It is rapidly metabolised, with an absolute bioavailability of about 3% of the oral dose, and a terminal half-life of 12 to 13 hours. Unlike other androgens (see Testosterone, p. 2308.3), mesterolone is not metabolised to oestrogenic compounds. Mesterolone is bound to serum proteins; about 40% to albumin and 58% to sex-hormone binding globulin. About 77% of the metabolites are excreted in the urine, and about 13% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Proviron; ***Austria***: Proviron; ***Belg.***: Proviron; ***Braz.***: Proviron; ***Chile***: Proviron; ***Cz.***: Proviron; ***Gr.***: Proviron; ***Hung.***: Proviron; ***India***: Mestilon; Provironum; ***Indon.***: Androlon†; Infelon; Proviron; ***Israel***: Proviron; ***Ital.***: Proviron; ***Malaysia***: Malvinum; Provironum; ***Mex.***: Proviron; ***Philipp.***: Proviron; Restore; ***Pol.***: Proviron; ***Port.***: Proviron; ***S.Afr.***: Proviron; ***Singapore***: Provironum; Restore; ***Spain***: Proviron; ***Thai.***: Mesviron; Provironum; ***Turk.***: Proviron; ***UK***: Proviron; ***Ukr.***: Proviron (Провирон); ***Venez.***: Proviron.

Multi-ingredient Preparations. ***Rus.***: Proviron (Провирон).

Mestranol (BAN, USAN, rINN)

Compound 33355; EE_3ME; Ethinyloestradiol-3-methyl Ether; Mestranolł; Mestranolis; Mestranolum; Mesztranol; Местранол.

3-Methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17β-ol.

$C_{21}H_{26}O_2$=310.4

CAS — 72-33-3.

UNII — B2V233XGE7.

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

Ph. Eur. 8: (Mestranol). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Mestranol). A white to creamy-white, odourless, crystalline powder. Insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in chloroform; soluble in dioxan; slightly soluble in methyl alcohol. Protect from light.

Uses and Administration

Mestranol is a synthetic oestrogen prodrug that is rapidly metabolised to ethinylestradiol; it therefore has actions similar to those of estradiol (see p. 2271.2). It is used as the oestrogen component of combined oral contraceptive preparations (see p. 2231.3) in a usual dose of 50 micrograms daily. The progestogen component is often norethisterone. Mestranol has also been used as the oestrogen component of some preparations for menopausal HRT (see p. 2244.2), although natural oestrogens are often preferred. It has been given in a sequential regimen in a dose of 50 micrograms daily, with a cyclical progestogen.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Interactions

See under Hormonal Contraceptives, p. 2242.3, and Hormone Replacement Therapy, p. 2251.1.

Pharmacokinetics

Mestranol is readily absorbed from the gastrointestinal tract, and about 70% is rapidly metabolised in the liver to ethinylestradiol (p. 2276.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Norinyl-1; ***Chile***: Anovulatorios; ***Ger.***: Esticia†; ***Hong Kong***: Norinyl-1†; ***Mex.***: Lutoral-E; Norace; Norinyl; Secuentex-21; ***NZ***: Norinyl-1; ***S.Afr.***: Norinyl-1/28; ***Thai.***: Anamal; ***UK***: Norinyl-1; ***USA***: Necon 1/50; Norinyl 1 + 50; Ortho-Novum 1/50†.

Pharmacopoeial Preparations

USP 36: Ethynodiol Diacetate and Mestranol Tablets; Norethindrone and Mestranol Tablets.

Metenolone (BAN, rINN) ⊗

Metenolon; Metenolona; Métenolone; Metenoloni; Metenolonum; Methenolone; Метенолон.

17β-Hydroxy-1-methyl-5α-androst-1-en-3-one.

$C_{20}H_{30}O_2$=302.5

CAS — 153-00-4.

ATC — A14AA04.

ATC Vet — QA14AA04.

UNII — 9062ZTBQ5C.

Metenolone Acetate (BANM, rINNM) ⊗

Acetato de metenolona; Acetato de metildrostenolona; Metenolona, acetato de; Métenolone, Acétate de; Metenoloni Acetas; Methenolone Acetate (USAN); Methenolone Acetate; NSC-74226; SH-567; SQ-16496; Метенолона Ацетат.

17β-Hydroxy-1-methyl-5α-androst-1-en-3-one acetate.

$C_{22}H_{32}O_3$=344.5

CAS — 434-05-9.

ATC — A14AA04.

ATC Vet — QA14AA04.

UNII — W75590VPKC.

Pharmacopoeias. In *Jpn*.

Metenolone Enantate (BANM, rINNM) ⊗

Enantato de metenolona; Enantato de metildrostenolona; Metenolona, enantato de; Métenolone, Enantate de; Metenoloni Enantas; Methenolone Enanthate (USAN); Methenolone Oenanthate; NSC-64967; SH-601; SQ-16374; Метенолона Энантат.

17β-Hydroxy-1-methyl-5α-androst-1-en-3-one heptanoate.

$C_{27}H_{42}O_3$=414.6

CAS — 303-42-4.

ATC — A14AA04.

ATC Vet — QA14AA04.

UNII — 0SPD480WFH.

Pharmacopoeias. In *Jpn*.

Profile

Metenolone is an anabolic steroid (see Testosterone, p. 2305.1) that has been used in treating aplastic anaemia, breast cancer, and postmenopausal osteoporosis. Metenolone acetate has been given in oral doses of 2 to 3 mg/kg daily for aplastic anaemia. Intramuscular depot injections of metenolone enantate have been given for osteoporosis in doses of 100 mg every 2 weeks, reducing to once every 3 to 4 weeks after an initial response. The acetate was also used orally in the past for osteoporosis. Intramuscular injections of 100 mg of the enantate every 1 to 2 weeks, or 200 mg every 2 to 3 weeks, have been used in progressive breast cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Primobolan†; ***Gr.***: Primobolan; ***Mex.***: Primobolan; ***S.Afr.***: Primobolan; ***Spain***: Primobolan Depot; ***Turk.***: Primobolan.

Homoeopathic Preparations. ***Ger.***: NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†.

Methandienone (BAN) ⊗

Metandienon; Metandienona; Metandienone (pINN); Metandienone; Metandienoni; Metandienonum; Methandrostenolone; NSC-42725; Метандиенон.

17β-Hydroxy-17α-methylandrosta-1,4-dien-3-one.

$C_{20}H_{28}O_2$=300.4

CAS — 72-63-9.

ATC — A14AA03; D11AE01.

ATC Vet — QA14AA03; QD11AE01.

UNII — C0Z187E0CC.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methandienone:

Iron Brew.

Pharmacopoeias. In *Pol.*

Uses and Administration

Methandienone has anabolic and some androgenic properties (see Testosterone, p. 2305.2). It has little progestogenic activity. Methandienone has been given orally as an anabolic drug. It has been subject to abuse in sport.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

As with other 17α-alkylated compounds, methandienone is associated with hepatotoxicity and hepatic function should be monitored during therapy. It should probably be avoided in patients with hepatic impairment, and certainly if this is severe.

Virilisation was reported[1] in 2 children, one of whom also developed adrenal suppression, after being given an 'appetite stimulant' containing methandienone and cyproheptadine.

1. **Poomthavorn P, *et al.* Childhood virilization and adrenal suppression after ingestion of methandienone and cyproheptadine. *J Pediatr Endocrinol Metab* 2009; 22: 459–62.**

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p. 2308.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Metanabol; ***Thai.***: Anabol; Dronabol; Melic†; Methandon.

Methyl-1-testosterone ⊗

17β-Hydroxy-17α-methyl-5α-androst-1-en-3-one; M1T; Метил-1-тестостерон.

$C_{20}H_{30}O_2$=302.5

CAS — 65-04-3.

Profile

Methyl-1-testosterone is an anabolic steroid (see Testosterone, p. 2305.1) that appears to be widely abused by body-builders.

References.

1. **Health Canada. Health Canada warns consumers not to use supplements containing methyl-1-testosterone due to potential serious health risks (issued February 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2006/2006_06-eng.php (accessed 19/07/10)**

Methyltestosterone (BAN, rINN) ⊗

Methyltestosteron; Méthyltestostérone; Methyltestosterónum; Metiltestosterona; Metiltesztoszteron; Metylotestosteron; Metyltestosteron; Metyylitestosteroni; NSC-9701; Метилтестостерон.

17β-Hydroxy-17α-methylandrost-4-en-3-one.

$C_{20}H_{30}O_2$=302.5

CAS — 58-18-4.

ATC — G03BA02.

ATC Vet — QG03BA02; QG03EK01.

UNII — V9EFU16ZJF.

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

Ph. Eur. 8: (Methyltestosterone). A white or slightly yellowish-white, crystalline powder. Practically insoluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Methyltestosterone). White or creamy-white, odourless, slightly hygroscopic, crystals or crystalline powder. Practically insoluble in water; soluble in alcohol,

in ether, in methyl alcohol, and in other organic solvents; sparingly soluble in vegetable oils. Protect from light.

Uses and Administration

As for androgens and anabolic steroids in general (see Testosterone, p. 2305.2).

Methyltestosterone is effective when given orally; its effect is increased about twofold when given buccally, as this avoids first-pass hepatic metabolism.

Suggested doses of methyltestosterone for androgen replacement therapy in male hypogonadism (p. 2252.3) have been 10 to 50 mg daily orally or 5 to 25 mg daily buccally. Doses of 50 to 200 mg daily orally or 25 to 100 mg daily buccally have been given for metastatic breast carcinoma (p. 702.1) in postmenopausal women. Oral doses of 1.25 to 2.5 mg daily, for 21 days of a 28-day cycle, have been given with oestrogens for the short-term treatment of menopausal vasomotor symptoms (p. 2245.1) unresponsive to oestrogens alone.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

As with other 17α-alkylated compounds, methyltestosterone can produce a cholestatic hepatitis with jaundice, and has caused peliosis hepatis and hepatic neoplasms (see below). Methyltestosterone should be used with caution in patients with liver impairment, and is probably best avoided if this is severe. Liver function should be monitored during therapy.

Effects on the liver. Reports of peliosis hepatis[1] and liver damage[2-4] associated with methyltestosterone.

See also under Malignant Neoplasms, below.

1. Bagheri SA, *et al.* Peliosis hepatis associated with androgenic-anabolic steroid therapy: a severe form of hepatic injury. *Ann Intern Med* 1974; 81: 610–18.
2. Westaby D, *et al.* Liver damage from long-term methyltestosterone. *Lancet* 1977; ii: 261–3.
3. Lowdell CP, Murray-Lyon IM. Reversal of liver damage due to long term methyltestosterone and safety of non-17 α -alkylated androgens. *BMJ* 1985; 291: 637.
4. Borhan-Manesh F, Farnum JB. Methyltestosterone-induced cholestasis: the importance of disproportionately low serum alkaline phosphatase level. *Arch Intern Med* 1989; 124: 2127–9.

MALIGNANT NEOPLASMS. Hepatocellular carcinoma[1-7] and hepatic adenoma[3,8] have been associated with methyltestosterone. A review[9] of reports of liver tumours associated with anabolic androgens found that methyltestosterone was an androgen that had been commonly implicated, and that the majority of tumours were hepatocellular carcinomas.

1. Johnson FL, *et al.* Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 1972; ii: 1273–6.
2. Henderson JT, *et al.* Androgenic-anabolic steroid therapy and hepatocellular carcinoma. *Lancet* 1973; i: 934.
3. Farrell GC, *et al.* Androgen-induced hepatoma. *Lancet* 1975; i: 430–2.
4. Goodman MA, Laden AMJ. Hepatocellular carcinoma in association with androgen therapy. *Med J Aust* 1977; i: 220–1.
5. Boyd PR, Mark GJ. Multiple hepatic adenomas and a hepatocellular carcinoma in a man on oral methyl testosterone for eleven years. *Cancer* 1977; 40: 1765–70.
6. Cocks JR. Methyltestosterone-induced liver-cell tumours. *Med J Aust* 1981; 2: 617–19.
7. Gleeson D, *et al.* Androgen associated hepatocellular carcinoma with an aggressive course. *Gut* 1991; 32: 1084–6.
8. Coombes GB, *et al.* An androgen-associated hepatic adenoma in a transsexual. *Br J Surg* 1978; 65: 869–70.
9. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; 77: 257–67.

Pregnancy. For reference to virilisation of a female fetus whose mother received methyltestosterone during pregnancy, see p. 2308.3.

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p. 2308.3).

Pharmacokinetics

Methyltestosterone is absorbed from the gastrointestinal tract and from the oral mucosa. It undergoes less extensive first-pass hepatic metabolism than testosterone after oral doses, and has a longer half-life.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Teston; *Thai.*: Metesto; *Turk.*: Afro; *USA*: Android; Testred; Virilon.

Multi-ingredient Preparations. *Chile*: Delitan; Feminova-T†; *Hong Kong*: Sessoforte†; Wari-Procomil†; *India*: Mixogen; *Mex.*: Bigenol†; *Thai.*: Men Hormone Compound; *UK*: Prowess; *USA*: Covaryx; Estratest†; Syntest.

Pharmacopoeial Preparations

USP 36: Methyltestosterone Capsules; Methyltestosterone Tablets.

Mibolerone *(BAN, USAN, rINN)* ⊗

Mibolerona; Mibolérone; Miboleronum; NSC-72260; U-10997; Мибоперон.

17β-Hydroxy-7α,17-dimethylestr-4-en-3-one.

$C_{20}H_{30}O_2$=302.5

CAS — 3704-09-4.

UNII — 9OGY48OR8D.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Mibolerone). A white to off-white powder. Practically insoluble in water; slightly soluble in chloroform, in dioxan, and in dichloromethane.

Profile

Mibolerone is an androgen that is used in veterinary practice as a contraceptive for female dogs. It also has anabolic properties.

Nafarelin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de nafarelina; Nafarelíiniasetaatti; Nafarelin Asetat; Nafarelina, acetato de; Nafarelinacetat; Nafaréline, Acétate de; Nafarelini Acetas; D-Nal(2)^6-LHRH acetate hydrate; RS-94991298; Нафарелина Ацетат.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-L-prolylglycinamide acetate hydrate.

$C_{66}H_{83}N_{17}O_{13}xC_2H_4O_2yH_2O$=1322.5 (nafarelin)

CAS — 76932-56-4 (nafarelin); 86220-42-0 (nafarelin acetate).

ATC — H01CA02.

ATC Vet — QH01CA02.

UNII — 8ENZ0QJW4H.

Uses and Administration

Nafarelin acetate is an analogue of gonadorelin (p. 2280.3) with similar properties. It is used in the treatment of endometriosis and central precocious puberty, and as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility.

For **endometriosis** it is given in usual doses equivalent to 200 micrograms of nafarelin twice daily intranasally, doubled after 2 months if amenorrhoea has not occurred. Treatment should begin on days 2 to 4 of the menstrual cycle, and may be continued for up to 6 months.

Regimens for **oocyte collection for IVF** use gonadorelin analogues for pituitary desensitisation before ovulation induction with gonadotrophins; the equivalent of 400 micrograms of nafarelin is given intranasally twice daily, beginning either in the early follicular phase (day 2) or midluteal phase (day 21) of the menstrual cycle. Therapy should be continued until downregulation is achieved; if this does not occur within 12 weeks therapy should be withdrawn. Once downregulation occurs gonadotrophin treatment is added to nafarelin therapy until an appropriate stage of follicular development, when both are withdrawn and chorionic gonadotrophin is given to induce ovulation.

Nafarelin has also been given in other sex hormone-related conditions.

The derivative azagly-nafarelin is used in veterinary medicine.

Administration in children. *Nafarelin may be used in the management of central precocious puberty—see below.*

Benign prostatic hyperplasia. For a discussion of the management of benign prostatic hyperplasia, including mention of the use of gonadorelin analogues and the view that they are unsatisfactory for indefinite therapy, see p. 2347.1.

Prostate size decreased by a mean of 24.2% in 9 men treated for benign prostatic hyperplasia for 6 months with nafarelin acetate 400 micrograms daily subcutaneously.[1] Six months after the end of treatment, prostate size approached that of pretreatment values.

1. Peters CA, Walsh PC. The effect of nafarelin acetate, a luteinizing-hormone-releasing hormone agonist, on benign prostatic hyperplasia. *N Engl J Med* 1987; 317: 599–604.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p. 2264.1), but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References to the use of nafarelin.

1. Henzl MR, *et al.* Administration of nasal nafarelin as compared with oral danazol for endometriosis: a multicenter double-blind comparative clinical trial. *N Engl J Med* 1988; 318: 485–9.
2. Burry KA. Nafarelin in the management of endometriosis: quality of life assessment. *Am J Obstet Gynecol* 1992; 166: 735–9.
3. Hornstein MD, *et al.* Retreatment with nafarelin for recurrent endometriosis symptoms: efficacy, safety, and bone mineral density. *Fertil Steril* 1997; 67: 1013–18.
4. Adamson GD, *et al.* Therapeudc efficacy and bone mineral density response during and following a three-month re-treatment of endometriosis with nafarelin (Synarel). *Am J Obstet Gynecol* 1997; 177: 1413–18.
5. Agarwal SK, *et al.* Nafarelin vs. leuprolide acetate depot for endometriosis: changes in bone mineral density and vasomotor symptoms. *J Reprod Med* 1997; 42: 413–23.
6. Zhao SZ, *et al.* Impact of nafarelin and leuprolide for endometriosis on quality of life and subjective clinical measures. *J Reprod Med* 1999; 44: 1000–1006.
7. Bergqvist A, *et al.* A comparative study of the acceptability and effect of goserelin and nafarelin on endometriosis. *Gynecol Endocrinol* 2000; 14: 425–32.
8. Cheng MH, *et al.* A randomized, parallel, comparative study of the efficacy and safety of nafarelin versus danazol in the treatment of endometriosis in Taiwan. *J Chin Med Assoc* 2005; 68: 307–14.

Fibroids. Gonadorelin analogues have been tried as an adjunct or alternative to surgery in the treatment of uterine fibroids (see p. 2281.2), although there has been some concern that this might complicate the diagnosis of malignancy.

References to the use of nafarelin.

1. Minaguchi H, *et al.* Clinical use of nafarelin in the treatment of leiomyomas: a review of the literature. *J Reprod Med* 2000; 45: 481–9.

Infertility. Gonadorelin analogues are used in the treatment of infertility (p. 2253.1): As well as being used directly they are employed in regimens to induce superovulation to enable ova collection and IVF. A meta-analysis[1] found that the outcome of IVF treatment using nafarelin was equivalent to that using other gonadorelin analogues, but that nafarelin was associated with a shorter time needed for ovarian stimulation and a reduced gonadotrophin requirement.

1. Wong JM, *et al.* Efficacy of nafarelin in assisted reproductive technology: a meta-analysis. *Hum Reprod Update* 2001; 7: 92–101.

Porphyria. Nafarelin nasal spray was used to prevent premenstrual exacerbations of acute intermittent porphyria (p. 1556.1) in 2 sisters.[1]

1. McNulty SJ, Hardy KJ. Two patients with acute intermittent porphyria treated with nafarelin to prevent menstrual exacerbations. *J R Soc Med* 2000; 93: 429–30.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p. 2254.1). The usual dose of nafarelin acetate is the equivalent of nafarelin 800 micrograms intranasally (400 micrograms in each nostril) twice daily. If adequate suppression is not achieved at this dose it may be increased to 600 micrograms three times daily in alternate nostrils (1800 micrograms daily).

References to the use of nafarelin.

1. Kreiter M, *et al.* Preserving adult height potential in girls with idiopathic true precocious puberty. *J Pediatr* 1990; 117: 364–70.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1.

Effects on electrolytes. Severe hyperkalaemia occurred in a woman receiving nafarelin therapy for uterine fibroids.[1] Despite serum-potassium greater than 10 mmol/litre she had no symptoms and the electrocardiogram was normal. Hyperkalaemia resolved without treatment on stopping nafarelin.

1. Hata T, *et al.* Severe hyperkalaemia with nafarelin. *Lancet* 1996; 347: 333.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nafarelin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1] For the use of nafarelin in the prevention of premenstrual exacerbations of acute porphyria, see above.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for Gonadorelin, p. 2282.2.

Pharmacokinetics

Nafarelin is rapidly absorbed on intranasal use and peak plasma concentrations occur within 20 minutes of a dose, although bioavailability is only about 3%. The plasma half-life is about 3 to 4 hours. Nafarelin is metabolised by peptidases in the body; after subcutaneous dosage it is excreted in urine, as metabolites and a small amount of unchanged drug, and in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Synrelin; *Austral.*: Synarel; *Braz.*: Synarel; *Canad.*: Synarel; *Cz.*: Synarel; *Denm.*: Synarel; Synarela; *Fin.*: Synarela; *Fr.*: Synarel; *Ger.*: Synarela; *Gr.*: Synarel; *India*: Nasarel; *Irl.*: Synarel; *Israel*: Synarel; *Neth.*: Synarel; *Norw.*: Synarela; *Pol.*: Synarel†; *S.Afr.*: Synarel†; *Spain*: Synarel; *Swed.*: Synarela; *Switz.*: Synrelina; *Turk.*: Synarel; *UK*: Synarel; *USA*: Synarel.

Nandrolone *(BAN, rINN)* ⊗

Estrenolona; Hidroxiestrenona; Nandrolon; Nandrolona; Nandrolone; Nandrolonum; Norandrostenolona; 19-Nortestosterone; Nortestrionato; Нандролон.
17β-Hydroxyestr-4-en-3-one; 3-Oxoestr-4-en-17β-yl.
$C_{18}H_{26}O_2$=274.4
CAS — 434-22-0.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.
UNII — 6PG9VR430D.

Nandrolone Cyclohexylpropionate *(BANM, rINNM)* ⊗

Ciclohexilpropionato de nandrolona; Nandrolona, ciclohexilpropionato de; Nandrolone Cyclohexanepropionate; Nandrolone, Cyclohexylpropionate de; Nandroloni Cyclohexylpropionas; Nortestosterone Cyclohexylpropionate; Нандролона Циклогексилпропионат.
3-Oxoestr-4-en-17β-yl 3-cyclohexylpropionate; 17β-Hydroxyestr-4-en-3-one cyclohexylpropionate.
$C_{27}H_{40}O_3$=412.6
CAS — 912-57-2.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.
UNII — K4NE48GG1Y.

Nandrolone Decanoate *(BANM, USAN, rINNM)* ⊗

Decanoato de nandrolona; Nandrolona, decanoato de; Nandrolondecanoat; Nandrolon-dekanoát; Nandrolone, décanoate de; Nandroloni Decanoas; Nandrolonu dekanonian; Nortestosterone Decanoate; Nortestosterone Decylate; Нандролона Деканоат.
3-Oxoestr-4-en-17β-yl decanoate; 17β-Hydroxyestr-4-en-3-one decanoate.
$C_{28}H_{44}O_3$=428.7
CAS — 360-70-3.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.
UNII — H45187T098.

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

Ph. Eur. 8: (Nandrolone Decanoate). A white or almost white, crystalline powder. M.p. 34 degrees to 38 degrees. Practically insoluble in water; very soluble in alcohol and in dichloromethane. Store under nitrogen at 2 degrees to 8 degrees. Protect from light.

USP 36: (Nandrolone Decanoate). A white to creamy-white fine crystalline powder, odourless or may have a slight odour. Practically insoluble in water; soluble in alcohol, in acetone, in chloroform, and in vegetable oils. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Nandrolone Laurate *(BANM, rINNM)* ⊗

Dodecanoato de nandrolona; Laurato de nandrolona; Nandrolona, laurato de; Nandrolone Dodecanoate; Nandrolone, Laurate de; Nandroloni Lauras; Nortestosterone Laurate; Нандролона Лаурат.
3-Oxoestr-4-en-17β-yl dodecanoate; 17β-Hydroxyestr-4-en-3-one dodecanoate.
$C_{30}H_{48}O_3$=456.7
CAS — 26490-31-3.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2014: (Nandrolone Laurate). A white to creamy-white crystalline powder. Practically insoluble in water; freely soluble in alcohol, in chloroform, in ether, in fixed oils, and in esters of fatty acids. Store at 2 degrees to 8 degrees. Protect from light.

Nandrolone Phenylpropionate *(BANM, rINNM)* ⊗

Fenilpropionato de nandrolona; Nandrolona, fenilpropionato de; Nandrolone Hydrocinnamate; Nandrolone Phenpropionate; Nandrolone, Phénylpropionate de; Nandroloni Phenylpropionas; Nandrolonu fenylopropionian; 19-Norandrostenolone Phenylpropionate; Nortestosterone Phenylpropionate; NSC-23162; Нандролона Фенилпропионат.
3-Oxoestr-4-en-17β-yl 3-phenylpropionate; 17β-Hydroxyestr-4-en-3-one 3-phenylpropionate.
$C_{27}H_{34}O_3$=406.6
CAS — 62-90-8.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.
UNII — KFZ29KZ13W.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of nandrolone phenylpropionate:
Iron Brew.

Pharmacopoeias. In *Br.*, *Chin.*, *Pol.*, and *US.*

BP 2014: (Nandrolone Phenylpropionate). A white to creamy-white crystalline powder with a characteristic odour. Practically insoluble in water; soluble in alcohol. Protect from light.

USP 36: (Nandrolone Phenpropionate). Store in airtight containers. Protect from light.

Nandrolone Sodium Sulfate *(BANM, rINNM)* ⊗

Nandrolona, sulfato sódico de; Nandrolone Sodium Sulphate; Nandrolone, Sulfate Sodique de; Nandroloni Natrii Sulfas; Nortestosterone Sodium Sulphate; Sulfato sódico de nandrolona; Нандролона Натрия Сульфат.
3-Oxoestr-4-en-17β-yl sodium sulphate; 17β-Hydroxyestr-4-en-3-one sodium sulphate.
$C_{18}H_{25}O_5SNa$=376.4
CAS — 60672-82-4.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.
UNII — W945A5Q7XN.

Nandrolone Undecylate *(rINNM)* ⊗

Nandrolona, undecilato de; Nandrolone Undecanoate (BANM); Nandrolone, Undécylate de; Nandroloni Undecylas; Nortestosterone Undecanoate; Undecilato de nandrolona; Нандролона Ундецилат.
3-Oxoestr-4-en-17β-yl undecanoate; 17β-Hydroxyestr-4-en-3-one undecanoate.
$C_{29}H_{46}O_3$=442.7
CAS — 862-89-5.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.
UNII — K64MCF119Z.

Uses and Administration

Nandrolone is an anabolic steroid with some androgenic properties (see Testosterone, p. 2305.2). It is usually given as the decanoate ester in the form of oily intramuscular injections. The hexyloxyphenylpropionate, propionate, phenylpropionate, and undecylate esters have also been used.

Doses of nandrolone decanoate 25 to 100 mg once every 3 to 4 weeks have been used as an anabolic after debilitating illness, for postmenopausal osteoporosis, and for postmenopausal metastatic breast carcinoma. Doses of between 50 and 200 mg weekly have been suggested for the treatment of anaemia of chronic renal failure, and doses of 50 to 150 mg weekly for aplastic anaemia.

Nandrolone sodium sulfate has been used topically in the treatment of corneal damage.

Nandrolone cyclohexylpropionate, laurate, and phenylpropionate are used in veterinary medicine.

Cachexia. Nandrolone increased lean body-mass in patients with HIV-associated wasting[1-4] (p. 959.1) and in one study[5] was found to have greater effect than testosterone on body-weight and BMI but a similar effect on lean body-mass. Nandrolone has also increased lean body-mass in patients with end-stage renal failure undergoing dialysis.[6,7] Although caution is generally advised with the use of androgenic and anabolic steroids in patients with renal impairment (see Testosterone, p. 2308.2), a study[8] of nandrolone given for 3 months to patients with predialysis chronic renal impairment found that lean body-mass increased without fluid retention or adverse effect on renal function or serum-lipids. In these reports, intramuscular doses of nandrolone decanoate have ranged from 100 mg once every 2 weeks[4] up to 600 mg weekly,[2] and treatment has generally been given for 12 to 24 weeks.

1. Gold J, *et al.* Safety and efficacy of nandrolone decanoate for treatment of wasting in patients with HIV infection. *AIDS* 1996 **10:** 745–52.
2. Sattler FR, *et al.* Effects of pharmacological doses of nandrolone decanoate and progressive resistance training in immunodeficient patients infected with human immunodeficiency virus. *J Clin Endocrinol Metab* 1999; **84:** 1268–76.
3. Storer TW, *et al.* A randomized, placebo-controlled trial of nandrolone decanoate in human immunodeficiency virus-infected men with mild to moderate weight loss with recombinant human growth hormone as active reference treatment. *J Clin Endocrinol Metab* 2005; **90:** 4474–82.
4. Mulligan K, *et al.* Effect of nandrolone decanoate therapy on weight and lean body mass in HIV-infected women with weight loss: a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med* 2005; **165:** 578–85.
5. Gold J, *et al.* Effects of nandrolone decanoate compared with placebo or testosterone on HIV-associated wasting. *HIV Med* 2006; **7:** 146–55.
6. Johansen KL, *et al.* Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. *JAMA* 1999; **281:** 1275–81.
7. Johansen KL, *et al.* Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. *J Am Soc Nephrol* 2006; **17:** 2307–14.
8. Eiam-Ong S, *et al.* Nutritional effect of nandrolone decanoate in predialysis patients with chronic kidney disease. *J Ren Nutr* 2007; **17:** 173–8.

Male contraception. Preliminary findings showed that nandrolone suppressed spermatogenesis,[1-3] suggesting potential as a male contraceptive (p. 2232.3), but later studies seem to have favoured other androgens.

1. Schürmeyer T, *et al.* Reversible azoospermia induced by the anabolic steroid 19-nortestosterone. *Lancet* 1984; **i:** 417–20.
2. Knuth UA, *et al.* Combination of 19-nortestosterone-hexyloxyphenylpropionate (Anadur) and depot-medroxyprogesterone-acetate (Clinovir) for male contraception. *Fertil Steril* 1989; **51:** 1011–18.
3. WHO Task Force on Methods for the Regulation of Male Fertility. Comparison of two androgens plus depot-medroxyprogesterone acetate for suppression to azoospermia in Indonesian men. *Fertil Steril* 1993; **60:** 1062–8.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

Abuse. Nandrolone, like other anabolic compounds, has been abused by athletes and bodybuilders. However, controversy has arisen over the methods used to detect abuse, and there is some evidence that metabolites of nandrolone may be produced endogenously (see under Precautions of Testosterone, p. 2308.2).

References.

1. Hemmersbach P, Grosse J. Nandrolone: a multi-faceted doping agent. *Handb Exp Pharmacol* 2010; **195:** 127–54.

Effects on the liver. Intrahepatic cholestasis occurred in a patient receiving nandrolone cyclohexylpropionate.[1]

1. Gil VG, *et al.* A non-C17-alkylated steroid and long-term cholestasis. *Ann Intern Med* 1986; **104:** 135–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nandrolone for systemic use as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1] It has not yet classified nandrolone for ophthalmic use.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p. 2308.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Deca-Durabolin; *Austral.*: Deca-Durabolin; *Austria*: Deca-Durabolin; *Belg.*: Deca-Durabolin; *Braz.*: Deca-Durabolin; *Canad.*: Deca-Durabolin†; *Chile*: Anaprolina; Deca-Durabolin; Nandrosande†; *Cz.*: Deca-Durabolin; Superanabolon†; *Fin.*: Deca-Durabolin; *Fr.*: Keratyl†; *Gr.*: Anaboline Depot; Anadurin; Deca-Durabolin; Elphihormo; Extraboline; Nurezan; Ziremilon; *Hong Kong*: Deca-Durabolin; *Hung.*: Retabolil; *India*: Abonic; Afdec; Alidec; Amdrec; Andysan; Aridron; Avillin; Beedec; Betabolin; Betadecabolin; Betalobin; Bonobol; Bonodec; Cadec; Cadesol; Canon; CNP; Conbol; Cudec; Curebol; DDLon; Dec-Ombolin; Deca Nandrobol; Deca-Arodec; Deca-Durabolin; Deca-Intabolin; Decamax; Decameribol; Decaneurabol; Decaneurophen; Decaras; Decarise; Decasoz; Decasun; Decatop; Decatrolin; Decaven; Decavillin; Decodeca; Decolane; Decolone; Deconbol; Decozoom; Decwell; Dekot; Dena-N; Destar; Drocan; Drona; Durabolin; Duras; Dynamax; Eldec; Esnadec; Foetacare; Fordec; HND; Idec; Indac; Indobol; Indodec; Indolone; Intradec; ITN; Kandrodec; Labdec; Megabol; Mendro; Metabol; Metadec; Metup; Mitydec; Multi-ND; Myobolin; N-Zol; Nabolin Dec; Nadrone; Nandodel; Nandro; Nandrobol; Nandrodec; Nandy; Nankair; Nanzon; NDMas; NDN; Neodec; Neurabol; Neurophen; Newbolin; Nikidac; Ninza; Nisdrol; NMX; Nubolin; Octobolin; Octodec; Osidec; *Indon.*: Deca-Durabolin; *Irl.*: Deca-Durabolin; *Ital.*: Deca-Durabolin; *Malaysia*: Deca-Durabolin; *Mex.*: Deca-Durabolin; *Neth.*: Deca-Durabolin; Durabolin†; *Norw.*: Deca-Durabolin†; *NZ*: Deca-Durabolin; *Pol.*: Deca-Durabolin; *Port.*: Deca-Durabolin; *Rus.*: Retabolil (Ретаболил); *S.Afr.*: Deca-Durabolin; *Singapore*: Deca-Durabolin; *Spain*: Deca-Durabolin; *Swed.*: Deca-Durabol†; *Switz.*: Deca-Durabolin; *Thai.*: Deca-Durabolin; Keratyl†; Nandro; *UK*:

Deca-Durabolin; *Ukr.*: Retabolil (Ретаболил); *USA*: Androlone-D; Deca-Durabolin; Durabolin; Hybolin; Neo-Durabolic; *Venez.*: Deca-Durabolin.

Multi-ingredient Preparations. *Gr.*: Docabolin†; *Indon.*: Dexatopic.

Pharmacopoeial Preparations
BP 2014: Nandrolone Decanoate Injection; Nandrolone Phenylpropionate Injection;
USP 36: Nandrolone Decanoate Injection; Nandrolone Phenpropionate Injection.

Nomegestrol Acetate *(BANM, USAN, rINNM)*

Acetato de nomegestrol; Nomegestrol acetát; Nomégestrol, acétate de; Nomegestrol, acetato de; Nomegestrol Asetat; Nomegestrolacetat; Nomegestroli Acetas; Nomegestroliasetaatti; Nomegestrolio acetatas; Nomegesztrol-acetát; Org-10486-0; TX-066; Номегестрона Ацетат.

17-Hydroxy-6-methyl-19-norpregna-4,6-diene-3,20-dione acetate.

$C_{23}H_{30}O_4$=370.5

CAS — 58691-88-6 (nomegestrol); 58652-20-3 (nomegestrol acetate).

ATC — G03DB04.

ATC Vet — QG03DB04.

UNII — 83J78V5W05.

NOTE. The name Uniplant has been used as a trade mark for nomegestrol acetate.

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

Ph. Eur. 8: (Nomegestrol Acetate). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone. Protect from light.

Profile

Nomegestrol acetate is a progestogen structurally related to progesterone (p. 2300.2) that has been used in the treatment of menstrual disorders and as the progestogen component of menopausal HRT (p. 2244.1) and combined oral hormonal contraceptives (see p. 2231.3). An oral dose of nomegestrol acetate for menstrual disorders is 5 mg daily for 10 days (from day 16 to day 25 of the cycle). For HRT, typical daily doses are 3.5 to 5 mg given for 12 to 14 days of a 28-day cycle. When used in monophasic combined oral contraceptive preparations, a dose of 2.5 mg may be given daily for 24 days of each 28-day cycle. A subdermal implant is under investigation as a long-acting progestogen-only contraceptive.

References.
1. Coutinho EM, *et al.* Multicenter clinical trial on the efficacy and acceptability of a single contraceptive implant of nomegestrol acetate, Uniplant. *Contraception* 1996; 53: 121–5.
2. Devoto L, *et al.* Hormonal profile, endometrial histology and ovarian ultrasound assessment during 1 year of nomegestrol acetate implant (Uniplant). *Hum Reprod* 1997; 12: 708–13.
3. Barbosa IC, *et al.* Carbohydrate metabolism in sickle cell patients using a subdermal implant containing nomegestrol acetate (Uniplant). *Contraception* 2001; 63: 263–5.
4. Arowojolu AO, Ladipo OA. Nonmenstrual adverse events associated with subdermal contraceptive implants containing normegestrel [sic] and levonorgestrel. *Afr J Med Med Sci* 2003; 32: 27–31.
5. Barbosa IC, *et al.* Effects of a single Silastic contraceptive implant containing nomegestrol acetate (Uniplant) on endometrial morphology and ovarian function for 1 year. *Contraception* 2006; 74: 492–7.
6. Lello S. Nomegestrol acetate: pharmacology, safety profile and therapeutic efficacy. *Drugs* 2010; 70: 541–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lutenyl; *Belg.*: Lutenyl; Nogest; *Braz.*: Lutenil; *Chile*: Lutenyl; *Hong Kong*: Lutenyl; *Indon.*: Lutenyl; *Ital.*: Lutenyl; *Mex.*: Luvenyl; *Mon.*: Lutenyl; *Pol.*: Lutenyl; *Port.*: Lutenyl; *Turk.*: Lutenyl; *Ukr.*: Lutenyl (Лютеніл).

Multi-ingredient Preparations. *Austral.*: Zoely; *Belg.*: Naemis; *Denm.*: Zoely; *Irl.*: IOA; Naemis†; Zoely; *Ital.*: Naemis; *Mon.*: Naemis; Zoely; *Neth.*: Ioa; Naemis†; Zoely; *Norw.*: Zoely; *Port.*: Naemis; *Spain*: Zoely; *Swed.*: Zoely; *Switz.*: Zoely; *UK*: Zoely.

Norelgestromin *(BAN, USAN, rINN)*

17-Deacylnorgestimate; Norelgestromiini; Norelgestromina; Norelgestromine; Norelgestrominum; RWJ-10553; Норэльгестромин.

13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime.

$C_{21}H_{29}NO_2$=327.5

CAS — 53016-31-2.

UNII — R0TAY3X631.

Profile

Norelgestromin is a progestogen (see Progesterone, p. 2300.2); it is the primary active metabolite of norgestimate (p. 2295.3). Norelgestromin is used as the progestogenic component of a combined contraceptive transdermal patch. About 203 micrograms of norelgestromin is released daily with ethinylestradiol. A new patch is applied each week for 3 weeks of a 4-week cycle. Norelgestromin exposure from such a patch may be greater than that resulting from a comparable oral contraceptive.

References.
1. Audet M-C, *et al.* Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. *JAMA* 2001; 285: 2347–54.
2. Abrams LS, *et al.* Pharmacokinetics of norelgestromin and ethinyl estradiol from two consecutive contraceptive patches. *J Clin Pharmacol* 2001; 41: 1232–7.
3. Abrams LS, *et al.* Pharmacokinetics of norelgestromin and ethinyl estradiol delivered by a contraceptive patch (Ortho Evra®/Evra®) under conditions of heat, humidity, and exercise. *J Clin Pharmacol* 2001; 41: 1301–9.
4. Abrams LS, *et al.* Pharmacokinetics of a contraceptive patch (Evra®/Ortho Evra®) containing norelgestromin and ethinyloestradiol at four application sites. *Br J Clin Pharmacol* 2002; 53: 141–6.
5. Burkman RT. The transdermal contraceptive system. *Am J Obstet Gynecol* 2004; 190 (suppl): S49–S53.
6. Devineni D, *et al.* Pharmacokinetics and pharmacodynamics of a transdermal contraceptive patch and an oral contraceptive. *J Clin Pharmacol* 2007; 47: 497–509.
7. Jick S, *et al.* Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 micrograms of ethinyl estradiol. *Contraception* 2007; 76: 4–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Evra; *Austria*: Evra; *Belg.*: Evra; *Braz.*: Evra; *Canad.*: Evra; *Chile*: Evra; *Cz.*: Evra; *Denm.*: Evra; *Fin.*: Evra; *Fr.*: Evra; *Ger.*: Evra; *Gr.*: Evra; *Hong Kong*: Evra; *Hung.*: Evra; *Irl.*: Evra; *Israel*: Evra; *Ital.*: Evra; *Malaysia*: Evra; *Mex.*: Evra; *Neth.*: Evra; *Norw.*: Evra; *Philipp.*: Evra; *Pol.*: Evra; *Port.*: Evra; *Rus.*: Evra (Espa); *S.Afr.*: Evra; *Singapore*: Evra; *Spain*: Evra; *Swed.*: Evra; *Switz.*: Evra; *Thai.*: Evra; *UK*: Evra; *USA*: Ortho Evra; *Venez.*: Evra.

Norethandrolone *(BAN, rINN)* ⊗

17α-Ethyl-17β-hydroxyestr-4-en-3-one; 17β-Hydroxy-19-nor-17α-pregn-4-en-3-one; Noretandrolona; Noréthandrolone; Norethandrolonum; Норэтандролон.

$C_{20}H_{30}O_2$=302.5

CAS — 52-78-8.

ATC — A14AA09.

ATC Vet — QA14AA09.

UNII — P7W01638W6.

Uses and Administration

Norethandrolone is an anabolic steroid with some androgenic properties (see Testosterone, p. 2305.2). It is given in the treatment of aplastic anaemia in an oral dose of 0.25 to 2 mg/kg daily.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3). As with other 17α-alkylated compounds, norethandrolone may produce hepatotoxicity and liver function should be monitored. It should probably be avoided in patients with impaired liver function, and certainly if this is severe.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Nilevar.

Norethisterone *(BAN, pINN)*

Ethinylnortestosterone; Etinil hidroxiestrona; Etinilnortestosterona; Norethindrone; Norethisteron; Noréthistérone; Norethisteronum; Noretindrona; Noretisteron; Noretisterona; Noretisteronas; Noretisterone; Noretisteroni; Noretiszteron; Noretysteron; Norpregneninolona; Norpregneninolone; NSC-9564; Норэтистерон.

17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one.

$C_{20}H_{26}O_2$=298.4

CAS — 68-22-4.

ATC — G03AC01; G03DC02.

ATC Vet — QG03AC01; QG03DC02.

UNII — T18F433X4S.

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

Ph. Eur. 8: (Norethisterone). A white or yellowish-white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in acetone; soluble in dichloromethane.

USP 36: (Norethindrone). A white to creamy-white odourless crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in chloroform and in dioxan; slightly soluble in ether.

Norethisterone Acetate *(BANM, pINNM)*

Acetato de noretisterona; Norethindrone Acetate; Norethisteronacetat; Norethisteron-acetát; Noréthistérone, Acétate de; Norethisteroni Acetas; Noretisteron Asetat; Noretisterona, acetato de; Noretisteronacetat; Noretisteroniasetaatti; Noretisterono acetatas; Noretiszteron-acetát; Норэтистерона Ацетат.

17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate; 3-Oxo-19-nor-17α-pregn-4-en-20-yn-17β-yl acetate.

$C_{22}H_{28}O_3$=340.5

CAS — 51-98-9.

ATC — G03AC01; G03DC02.

ATC Vet — QG03AC01; QG03DC02.

UNII — 9S44UC7OJ.

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

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

USP 36: (Norethindrone Acetate). A white to creamy-white odourless crystalline powder. Practically insoluble in water; soluble 1 in 10 of alcohol, 1 in less than 1 of chloroform, 1 in 2 of dioxan, and 1 in 18 of ether.

Norethisterone Enantate *(BANM, pINNM)*

Enantato de noretisterona; Norestisteron Enantat; Norethindrone Enanthate; Noréthistérone, Enantate de; Norethisterone Enanthate; Norethisterone Heptanoate; Norethisteroni Enantas; Noretisterona, enantato de; Норэтистерона Энантат.

17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one heptanoate.

$C_{27}H_{38}O_3$=410.6

CAS — 3836-23-5.

ATC — G03AC01; G03DC02.

ATC Vet — QG03AC01; QG03DC02.

UNII — HY3S2K0J0F.

Pharmacopoeias. In *Int.*

Uses and Administration

Norethisterone and its acetate and enantate esters are progestogens (see Progesterone, p. 2300.2) derived from nortestosterone that have weak oestrogenic and androgenic properties. They are commonly used as **hormonal contraceptives** (see p. 2231.3). Norethisterone and norethisterone acetate are both given orally. Typical daily doses are 350 micrograms for norethisterone and 600 micrograms for norethisterone acetate when used alone, or 0.5 to 1 mg for norethisterone and 1 to 1.5 mg for norethisterone acetate when used with an oestrogen. Norethisterone enantate is given by intramuscular injection; a dose of 200 mg provides contraception for 8 weeks. An intramuscular injection containing norethisterone enantate 50 mg with estradiol valerate 5 mg is given once each month.

Norethisterone and norethisterone acetate are used as the progestogen component of **menopausal HRT** (see p. 2244.2). Typical regimens have included either continuous daily doses of norethisterone 700 micrograms or norethisterone acetate 0.5 to 1 mg, or cyclical regimens of norethisterone or norethisterone acetate 1 mg daily for 10 to 12 days of a 28-day cycle. Norethisterone acetate is also available as transdermal patches supplying 140, 170, or 250 micrograms in 24 hours, that are applied twice weekly for 2 weeks of a 4-week cycle; the lower strengths may also be applied twice weekly on a continuous basis.

Norethisterone and norethisterone acetate may be given orally, usually in divided doses, for the treatment of conditions such as **menorrhagia** (p. 2295.1) and **endometriosis** (p. 2264.1). In menorrhagia (dysfunctional uterine bleeding), norethisterone is given in usual doses of 10 to 15 mg daily and norethisterone acetate in doses of 2.5 to 10 mg daily, in a cyclical regimen. In endometriosis the dosage of norethisterone is 10 to 25 mg daily and of norethisterone acetate 5 to 15 mg daily. Treatment of endometriosis is usually continuous for 4 to 9 months.

Norethisterone has been used in daily doses of up to 15 mg orally in a cyclical regimen in the treatment of **premenstrual syndrome** (p. 2272.3).

In **breast cancer** (p. 702.1) oral doses of up to 60 mg daily of norethisterone have been used.

For the use of norethisterone in children, see below.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* does include norethisterone for the management of delayed puberty (p. 2252.1) in girls. It is added after 12 to 24 months of

oestrogen therapy to establish a menstrual cycle and maintain sexual maturation, in an oral dose of 5 mg once daily for the last 7 days of a 28-day cycle.

Menorrhagia. Although cyclical norethisterone has been widely used for menorrhagia (p. 2300.3), it is of limited efficacy during ovulatory cycles[1] being most effective for anovulatory bleeding, which occurs in a minority of women with menorrhagia.

1. Lethaby A, *et al.* Cyclical progestogens for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Effects on the liver. There were 6 cases of jaundice among 107 patients with breast cancer treated with high-dose norethisterone acetate;[1] the jaundice was reversible and of an obstructive type. A retrospective analysis[2] found that the use of norethisterone to prevent menstrual haemorrhage during the thrombocytopenic phase of allogeneic bone marrow transplantation was a significant risk factor for hepatic veno-occlusive disease.

1. Langlands AO, Martin WMC. Jaundice associated with norethisterone-acetate treatment of breast cancer. *Lancet* 1975; i: 584–5.
2. Hägglund H, *et al.* Norethisterone treatment, a major risk-factor for veno-occlusive disease in the liver after allogeneic bone marrow transplantation. *Blood* 1998; 92: 4568–72.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies norethisterone 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 04/10/11)

Pregnancy. Abnormalities seen in the offspring of women given norethisterone during pregnancy (either alone or with ethinylestradiol) included: hypospadias,[1] masculinisation of female infants,[2] meningomyelocele or hydrocephalus,[3] and neonatal choreoathetosis associated with oral contraceptive use.[4] For reference to the fact that oral contraceptives have not generally been associated with teratogenicity, even when used inadvertently in pregnancy, see p. 2242.1.

1. Aarskog D. Clinical and cytogenetic studies in hypospadias. *Acta Paediatr Scand* 1970; (suppl 203): 1–62.
2. Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA* 1960; 172: 1028–32.
3. Gal I, *et al.* Hormonal pregnancy tests and congenital malformation. *Nature* 1967; 216: 83.
4. Profumo R, *et al.* Neonatal choreoathetosis following prenatal exposure to oral contraceptives. *Pediatrics* 1990; 86: 648–9.

Venous thromboembolism. For mention that combined oral contraceptives containing older progestogens such as norethisterone appear to be associated with a lower incidence of venous thromboembolism than desogestrel- or gestodene-containing preparations, see p. 2238.1.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

Norethisterone is absorbed from the gastrointestinal tract, undergoing first-pass hepatic metabolism and peak plasma concentrations occur 1 to 2 hours after an oral dose. It has biphasic pharmacokinetics; an initial distribution phase is followed by a prolonged elimination phase with a half-life of about 8 hours or more. Norethisterone is highly protein bound; about 60% to albumin and 35% to sex hormone binding globulin. Use with an oestrogen increases the proportion bound to sex hormone binding globulin. It is metabolised in the liver with 50 to 80% of a dose being excreted in the urine and up to 40% appearing in the faeces.

Norethisterone acetate is rapidly hydrolysed to norethisterone, mainly by intestinal tissue.

After intramuscular injection of norethisterone enantate peak concentrations of norethisterone in plasma are not attained for several days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ginediol; Primolut-Nor; Selectan; *Austral.*: Locilan; Micronor; Noriday; Primolut N; *Austria*: Micronovum; *Belg.*: Primolut-Nor; *Braz.*: Linatis; Micronor; Norestin; Primolut-Nor; *Canad.*: Micronor; Norlutate; *Chile*: Primolut-Nor†; *Denm.*: Mini-Pe; Noriday; Systen Conti; *Fin.*: Mini-Pill; Primolut N; Primolut-Nor; *Fr.*: Milligynon†; *Ger.*: Gestakadin†; Noristerat; Primolut-Nor†; *Gr.*: Fortilut; Primolut-Nor; Santalut; Vilcolut; *Hong Kong*: Norcolut; Norelut†; Primolut N†; *Hung.*: Norcolut; *India*: Amenova; Corolut-N; Cycloreg; Dub; Dubact; Ethisone; Gynut-N; Menor-N; Mensil-N; Norate; Noreta HRT; Norfast; Norgest; Norglen; Noristerat; Noritis; Norlut N; Nostra; Noteron; Primolut N; Styptin; *Indon.*: Anore; Norelut; Primolut N; Regumen; *Irl.*: Noriday; Primolut N; *Israel*: Primolut-Nor; *Ital.*: Primolut-Nor; *Malaysia*: Depocon; Norcolut; Norcutin; Noriday; Noristerat; Primolut N†; Sunolut; *Mex.*: Noristerat; Primolut-Nor; *Neth.*: Primolut N; *Norw.*: Conludag; Primolut N; *NZ*: Noriday; Primolut N; *Philipp.*: Noristerat†; Oretes; Primolut N; *Pol.*: Primolut-Nor; *Port.*: Primolut-Nor; *Rus.*: Norcolut (Норколут); Primolut-Nor (Примолют-нор)†; *S.Afr.*: Micro-Novum; Nur-Isterate; Primolut N; *Singapore*: Depocon; Micronor†; Norcolut; Norcutin; Primolut N; SP-Norvulin; Sunolut; *Spain*: Primolut-Nor; *Swed.*: Mini-Pe; Primolut-Nor; *Switz.*: Micronovum; Primolut N; *Thai.*: Norterone; Primolut N; Steron; Sunolut; *Turk.*: Primolut N; *UK*: Micronor; Noriday; Noristerat; Primolut N; Utovlan; *Ukr.*: Norcolut (Норколут); Primolut-Nor (Примолют-Нор); *USA*: Aygestin; Heather; Jencycla; Jolivette; Nor-QD; Ortho Micronor.

Multi-ingredient Preparations. *Arg.*: Activelle; Disequens; Estalis Sequi†; Estalis†; Estracomb†; Estragest; Evorel Conti; Evorel Sequi; Kliogest; Mesigyna; Primosiston; Trial Combi; Trial Gest; Trisequens; *Austral.*: Brevinor; Estalis Continuous; Estalis Sequi; Estracombi; Improvil; Kliogest; Kliovance; Norimin; Norinyl-1; Synphasic; Trisequens; *Austria*: Activelle; Duokliman; Estalis Sequens†; Estalis; Estracomb†; Kliogest; Mericomb; Merigest; Ovysmen; Perikliman; Primosiston; Sequidot 2-Phasen; Trinovum; Trisequens; *Belg.*: Activelle; Estalis; Estracombi; Kliogest; Novofem; Ovysmen; Trinovum; Trisequens; *Braz.*: Activelle; Ciclovulon; Cliane; Estalis SQ; Estalis; Estragest; Gineane; Kliogest; Mericomb; Merigest; Mesigyna; Natifa Pro; Noregyna; Primosiston; Suprelle; Suprema; Systen Conti; Systen Sequi; Trisequens; *Canad.*: Activelle; Brevicon; Estalis; Estracomb†; FemHRT; Loestrin 1.5/30; Minestrin; Ortho 0.5/35; Ortho 1/35; Ortho 7/7/7; Select 1/35; Synphasic; *Chile*: Activelle; Cliane; Enadiol Neta†; Estracomb†; Estragest; Ginefolin; Kliogest; Mesigyna; Primosiston; Trisequens; *China*: Activelle (诺更宁); Compound Norethisterone (复方炔诺酮); Novofem; Trisequens (诺康律); Yi Wei Xian (逸维仙); Yiketing (谊可婷); Cz.: Activelle; Estalis Sequi†; Estalis†; Gynovel; Kliane; Kliogest; Noviana; Novofem; Pausogest†; Sequidot†; Systen Conti; Systen Sequi; Trinovum; Trisequens; *Denm.*: Activelle; Cliovelle; Estracomb†; Evo-Conti; Evo-Sequi; Femanor; Femasekvens; Kliogest; Novofem; Trinovum†; Trisekvens; Trisequens; *Fin.*: Activelle; Cliovelle; Estalis Sekvens†; Estalis; Evorel Conti; Evorel Sequi; Kliogest; Mericomb†; Merigest†; Novofem; Sequidot; Trisekvens; *Fr.*: Activelle; Kliogest; Minephase†; Novofemme; Ortho-Novum 1/35†; Triella; Trisequens; *Ger.*: Activelle; Clionara; Cliovelle; Conceplan M; Estalis Sequi†; Estragest; Eve; Gynamon†; Kliogest N; Mericomb; Merigest; Novofem; Sequidot; Synphase; Trinovum; Trisequens; *Gr.*: Activelle; Estalis Sequi; Estalis Sequidot; Estalis; Estracomb TTS; Kliogest; Systen Conti; Systen Sequi; Trisequens; *Hong Kong*: Activelle; Estracomb†; Kliogest; Norinyl-1†; Novofem; Trisequens; *Hung.*: Activelle; Estracomb†; Estragest; Kliogest; Novofem; Pausogest; Triaklim; Trisequens; Tulita; *Irl.*: Activelle; Brevinor†; Estalis Sequi†; Estalis†; Estracomb†; Evorel Conti; Kliogest; Novofem; Trisequens; *Israel*: Activelle; Eviana; Evorel Conti; Evorel Sequi; Kliogest; Novofem; Trisequens; *Ital.*: Activelle; Estalis Sequi; Estracomb†; Kliogest; Trisequens; *Jpn*: Lunabell; Ortho 777; *Malaysia*: Activelle; *Mex.*: Cliane; Estalis†; Estracomb; Evorel Conti; Mesigyna; Norace; Norinyl; Nostidyn; Ortho-Novum 1/35; *Neth.*: Activelle; Estalis Sequi†; Estalis†; Estracomb†; Eviana; Kliogest; Modicon; Neocon; Novofem; Trinovum; Trisequens; *Norw.*: Activelle; Cliovelle; Estalis Sekvens†; Estalis; Eviana; Kliogest†; Novofem; Sequidot; Synfase; Trisekvens; *NZ*: Brevinor; Cliane†; Kliogest; Kliovance; Norimin; Norinyl-1; Synphasic; Trisequens; *Philipp.*: Kliogest; Micropil Plus; Micropil; *Pol.*: Activelle; Cliovelle; Estalis Sequi†; Estalis; Estracomb; Kliogest; Novofem; Systen Conti; Systen Sequi; Trinovum†; Trisequens; *Port.*: Activelle; Estalis Sequi; Estalis; Estracomb†; Kliogest; Novofem; Trisequens; *Rus.*: Kliogest (Клиогест); Non-Ovlon (Нон-овлон)†; Pausogest (Пауэогест); Triaklim (Триаклим); Trisequens (Трисеквенс); *S.Afr.*: Activelle; Estalis; Estracombi†; Estro-Pause N; Evorel Conti; Evorel Sequi; Kliogest; Norinyl-1/28; Novofem; Trinovum; Trisequens; *Singapore*: Activelle; Estracomb; Kliogest†; Trisequens; *Spain*: Absorlent Plus†; Activelle; Duofemme; Endomina Plus†; Estalis Sequi; Estalis; Estracomb†; Eviana; Merigest Sequi†; Merigest†; Trisequens; *Swed.*: Activelle; Cliovelle; Estalis; Eviana; Femanor; Femasekvens; Kliogest†; Novofem; Orthonett Novum; Sequidot; Synfase; Trinovum; Trisekvens†; *Switz.*: Activelle; Estalis Sequi†; Estalis; Estracomb†; Estragest; Estranor; Kliogest N; Mericomb†; Merigest†; Novofem; Primosiston†; Sequidot; Systen Conti; Systen Sequi; Trinovum; Trisequens; *Thai.*: Activelle; Anamai; Havina†; *Turk.*: Activelle; Estracombi; Kliogest; Mesigyna; Trisequens; *UK*: Binovum; Brevinor; Climagest; Climesse; Clinorette; Elleste Duet Conti; Elleste-Duet; Estracombi†; Evorel Conti; Evorel Sequi; Kliofem; Kliovance; Loestrin; Norimin; Norinyl-1; Novofem; Nuvelle Continuous; Ovysmen; Synphase; Trinovum; Trisequens; *Ukr.*: Pausogest (Пауэогест)†; Revmelid (Ревмелид)†; *USA*: Activella; Alyacen 1/35; Alyacen 7/7/7; Aranelle; Balziva; Brevicon; Briellyn; CombiPatch; Estrostep Fe; Femcon Fe; FemHRT; Jinteli; Junel Fe; Leena; Lo Loestrin Fe; Lo Minastrin Fe; Loestrin Fe; Loestrin; Lupaneta Pack; Mimvey; Minastrin 24 FE; Modicon; Necon 1/50; Necon 10/11; Necon 0.5/35, 1/35; NEE 1/35; Norinyl 1 + 35; Norinyl 1 + 50; Nortrel; Ortho-Novum 1/35; Ortho-Novum 1/50†; Ortho-Novum 10/11†; Ortho-Novum 7/7/7; Ovcon 35; Ovcon 50; Pirmella 1/35; Pirmella 7/7/7; Tilia Fe; Tri-Legest; Tri-Norinyl; Wymzya Fe; Zenchent Fe; Zenchent; *Venez.*: Cliane; Estragest; Mesigyna.

Pharmacopoeial Preparations

BP 2014: Estradiol and Norethisterone Acetate Tablets; Estradiol and Norethisterone Tablets; Norethisterone Tablets;

USP 36: Estradiol and Norethindrone Acetate Tablets; Norethindrone Acetate and Ethinyl Estradiol Tablets; Norethindrone Acetate Tablets; Norethindrone and Ethinyl Estradiol Tablets; Norethindrone and Mestranol Tablets; Norethindrone Tablets.

Noretynodrel (BAN, rINN)

Norethynodrel (USAN); Norethynodrel; Noretinodrel; Noretynodreel; Noretynodrel; Noretynodrelum; NSC-15432; SC-4642; Норэтинодрел.

17β-Hydroxy-19-nor-17α-pregn-5(10)-en-20-yn-3-one.

$C_{20}H_{26}O_2$=298.4

CAS — 68-23-5.

UNII — 88181ACA0M.

Profile

Noretynodrel is a progestogen (see Progesterone, p. 2300.2) structurally related to norethisterone that has been given orally with an oestrogen such as mestranol for the treatment of various menstrual disorders and endometriosis.

Breast feeding. About 1% of an oral dose of radiolabelled noretynodrel was detected in breast milk in a study of 4 women.[1] No adverse effects have been seen in breast-fed infants of mothers given noretynodrel, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Laumas KR, *et al.* Radioactivity in the breast milk of lactating women after oral administration of ^{3}H-norethynodrel. *Am J Obstet Gynecol* 1967; 98: 411–3.
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 27/06/08)

Pregnancy. A woman given noretynodrel during pregnancy to prevent threatened miscarriage gave birth to a female infant showing signs of masculinisation.[1]

1. Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA* 1960; 172: 1028–32.

Norgestimate (BAN, USAN, rINN)

D-13B; Dexnorgestrel Acetime; Norgestimaatti; Norgestimat; Norgestimato; Norgestimatum; ORF-10131; RWJ-10131; Норестимат.

13β-Ethyl-3-hydroxyimino-18,19-dinor-17α-pregn-4-en-20-yn-17β-yl acetate.

$C_{23}H_{31}NO_3$=369.5

CAS — 35189-28-7.

UNII — C291HFX4DY.

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

Ph. Eur. 8: (Norgestimate). A white or almost white powder. Practically insoluble in water; freely soluble in dichloromethane; soluble in acetone.

USP 36: (Norgestimate). A mixture of (*E*)- and (*Z*)-isomers having a ratio of (*E*)- to (*Z*)-isomer between 1.27 and 1.78. A white to pale yellow powder. Insoluble in water; sparingly soluble in acetonitrile; freely to very soluble in dichloromethane.

Profile

Norgestimate is a progestogen (see Progesterone, p. 2300.2) structurally related to levonorgestrel (to which it is partly metabolised) that is used as the progestogenic component of combined oral contraceptives (see p. 2231.3) and in menopausal HRT (see p. 2244.1). A typical daily dose is 250 micrograms in monophasic contraceptive preparations, and 180 to 250 micrograms in triphasic preparations. For HRT, a regimen of estradiol daily for 3 days followed by estradiol with norgestimate 90 micrograms daily for 3 days is used; this 6-day cycle is repeated continuously without interruption.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies norgestimate in combined hormonal contraceptives 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 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Cilest; Prefest; Tridette; *Austria*: Cileste; TriCilest; Vivelle; *Belg.*: Cilest; *Braz.*: Prefest; *Canad.*: Cyclen; Tri-Cyclen; *Chile*: Mactex; Neofam†; Orlon; Tri-Mactex†; *Cz.*: Cilest; Pramino; *Denm.*: Cilest; *Fin.*: Cilest; *Fr.*: Cilest; Effiprev; Triafemi; TriCilest; *Ger.*: Cilest; Pramino; *Hung.*: Cilest; *Irl.*: Cilest; *Israel*: Ortho Cyclen; *Mex.*: Cilest; Prefest; *Neth.*: Cilest; *Pol.*: Cilest; *Rus.*: Cilest (Силест); *S.Afr.*: Cilest; Prefesta†; TriCilest; *Spain*: Edelsin; *Swed.*: Cilest; *Switz.*: Cilest; *Thai.*: Cilest; TriCilest; *UK*: Cilest; Lizinna; *USA*: Estaryla; Ortho Cyclen; Ortho Tri-Cyclen; Prefest; Previfem; Sprintec; Tri-Estarylla; Tri-Linyah; Tri-Lo-Sprintec; Tri-Previfem; Tri-Sprintec; TriNessa; *Venez.*: Ortrel.

Pharmacopoeial Preparations
USP 36: Norgestimate and Ethinyl Estradiol Tablets.

Norgestomet *(BAN, USAN, rINN)*

Norgestometum; SC-21009; Норгестомет.
11β-Methyl-3,20-dioxo-19-norpregn-4-en-17α-yl acetate.
$C_{23}H_{32}O_4$=372.5
CAS — 25092-41-5.
UNII — 3L33UD42X4.

Profile

Norgestomet is a progestogen (see Progesterone, p. 2300.2) used in veterinary medicine with estradiol.

Norgestrel *(BAN, USAN, rINN)*

dl-Norgestrel; Norgestreeli; DL-Norgestrel; Norgestrelis; Norgestrelum; Norgesztrel; Wy-3707; Норгестрел.
(±)-13-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.
$C_{21}H_{28}O_2$=312.5
CAS — 6533-00-2.
UNII — 3J8Q1747Z2.

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

Ph. Eur. 8: (Norgestrel). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Norgestrel). A white or practically white, practically odourless crystalline powder. Insoluble in water; sparingly soluble in alcohol; freely soluble in chloroform.

Levonorgestrel *(BAN, USAN, rINN)*

Levonorgestreeli; Lévonorgestrel; Levonorgestrelis; Levonorgestrelum; Levonorgesztrel; D-Norgestrel; Wy-5104; Левоноргестрел.
(-)-13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.
CAS — 797-63-7.
ATC — G03AD01.
ATC Vet — QG03AC03.
UNII — 5W7SIA7YZW.

NOTE. The name Dexnorgestrel has also been used.

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

Ph. Eur. 8: (Levonorgestrel). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Levonorgestrel). A white or practically white, odourless powder. Practically insoluble in water; slightly soluble in alcohol; soluble in chloroform. Protect from light.

Uses and Administration

Norgestrel and its active (-)-isomer levonorgestrel are progestogens (see Progesterone, p. 2300.2) derived from nortestosterone. They are more potent inhibitors of ovulation than norethisterone and have androgenic activity. Levonorgestrel is more commonly used than norgestrel and is twice as potent. For example, levonorgestrel 10 micrograms is equivalent to norgestrel 20 micrograms.

They are both used as **hormonal contraceptives** (see p. 2231.3). The typical daily dose is the equivalent of:

- 30 micrograms of levonorgestrel as an oral progestogen-only contraceptive
- 150 micrograms of levonorgestrel in monophasic combined oral contraceptives (doses may range from a low dose of 100 micrograms of levonorgestrel in some preparations up to 250 micrograms in others; a preparation containing 90 micrograms of levonorgestrel for continuous use without a tablet-free interval is also available)
- 50 to 125 micrograms of levonorgestrel in triphasic preparations

Subcutaneous implants containing levonorgestrel may be used for long-acting progestogen-only contraception. Insertion and removal must be carried out by personnel fully trained in the technique. One available product consists of 2 implants, each containing 75 mg of levonorgestrel. It should be inserted under the skin within the first 7 days of the menstrual cycle, and is effective for up to 5 years. Another product consisting of 6 implants, which also provided up to 5 years of contraception, is no longer widely marketed. Each implant contained 36 mg of levonorgestrel. Uterine, cervical, and vaginal devices containing levonorgestrel have also been investigated. One intra-uterine device (*Mirena, Bayer*) available for contraception contains a total of 52 mg of levonorgestrel, which is released at an initial rate of about 20 micrograms per 24 hours; the device is effective for 5 years. Another intra-uterine device (*Skyla, Bayer*) contains 13.5 mg of levonorgestrel, and releases an average of about 6 micrograms daily to provide contraception for 3 years.

For **emergency contraception** (p. 2233.2), levonorgestrel may be given alone in a single oral dose of 1.5 mg within 72 hours of coitus (preferably as soon as possible). Alternatively, a dose of 750 micrograms is given within 72 hours of coitus (preferably as soon as possible), and repeated after 12 hours. Another regimen uses levonorgestrel 500 micrograms plus ethinylestradiol 100 micrograms, given within 72 hours of coitus and repeated after 12 hours.

An intra-uterine device (*Mirena, Bayer*) is available for **menorrhagia** (below). It contains a total of 52 mg of levonorgestrel, which is released at an initial rate of 20 micrograms per 24 hours, and is effective for 5 years. Another treatment should be considered if bleeding does not improve within 3 to 6 months after insertion.

Both levonorgestrel and norgestrel are used as the progestogenic component of **menopausal HRT** (see p. 2244.2). Typical regimens are the equivalent of 75 to 250 micrograms of levonorgestrel orally for 10 to 12 days of a 28-day cycle. Levonorgestrel may also be given via a combined transdermal patch, releasing 10 micrograms per 24 hours, which is applied once weekly for 2 weeks of a 4-week cycle. Alternatively, a patch releasing 7 or 15 micrograms per 24 hours with an oestrogen is applied once weekly for continuous HRT. The intra-uterine device *Mirena*, as described above, may be used for up to 4 years with oestrogen replacement therapy.

Administration. *IMPLANTS.* Some references to the use of levonorgestrel by subcutaneous implant for hormonal contraception.[1-3]

1. Coukell AJ, Balfour JA. Levonorgestrel subdermal implants: a review of contraceptive efficacy and acceptability. *Drugs* 1998; 55: 861–87.
2. Sivin I. Risks and benefits, advantages and disadvantages of levonorgestrel-releasing contraceptive implants. *Drug Safety* 2003; 26: 303–35.
3. Power J, *et al.* Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).

INTRA-UTERINE DEVICES. Some references to the use of levonorgestrel-releasing intra-uterine devices for contraception[1-8] and menopausal HRT.[9,10]

1. Backman T, *et al.* Length of use and symptoms associated with premature removal of the levonorgestrel intrauterine system: a nationwide study of 17,360 users. *Br J Obstet Gynaecol* 2000; 107: 335–9.
2. French RS, *et al.* Levonorgestrel-releasing (20 microgram/day) intrauterine systems (Mirena) compared with other methods of reversible contraceptives. *Br J Obstet Gynaecol* 2000; 107: 1218–25.
3. Backman T. Benefit-risk assessment of the levonorgestrel intrauterine system in contraception. *Drug Safety* 2004; 27: 1185–1204.
4. Guillebaud J. The levonorgestrel intrauterine system: a clinical perspective from the UK. *Ann N Y Acad Sci* 2003; 997: 185–93.
5. Jensen JT. Contraceptive and therapeutic effects of the levonorgestrel intrauterine system: an overview. *Obstet Gynecol Surv* 2005; 60: 604–12.
6. Peled Y, *et al.* Levonorgestrel-releasing intrauterine system as an adjunct to estrogen for the treatment of menopausal symptoms—a review. *Menopause* 2007; 14: 550–4.
7. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. FSRH guidance (November 2007): intrauterine contraception. Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceIntrauterineContraceptionNov07.pdf (accessed 18/07/08)
8. Rose S, *et al.* Mirena (levonorgestrel intrauterine system): a successful novel drug delivery option in contraception. *Adv Drug Deliv Rev* 2009; 61: 808–12.
9. Sitruk-Ware R. The levonorgestrel intrauterine system for use in peri- and postmenopausal women. *Contraception* 2007; 75 (suppl): S155–S160.
10. Chrisman C, *et al.* The levonorgestrel-releasing intrauterine system: an updated review of the contraceptive and noncontraceptive uses. *Clin Obstet Gynecol* 2007; 50: 886–97.

Menorrhagia. Although oral cyclical progestogens have limited efficacy in the treatment of menorrhagia (p. 2300.3), a levonorgestrel-containing intra-uterine device appears to be particularly useful in reducing menstrual blood loss.[1-5]

1. Lethaby AE, *et al.* Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 06/09/13).
2. Kaunitz AM, *et al.* Levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: a systematic review and meta-analysis. *Obstet Gynecol* 2009; 113: 1104–16.
3. Kaunitz AM, Inki P. The levonorgestrel-releasing intrauterine system in heavy menstrual bleeding: a benefit-risk review. *Drugs* 2012; 72: 193–215.
4. Jensen J, *et al.* Bleeding patterns with the levonorgestrel-releasing intrauterine system when used for heavy menstrual bleeding in women without structural pelvic pathology: a pooled analysis of randomized controlled studies. *Contraception* 2013; 87: 107–12.
5. Gupta J, *et al.* ECLIPSE Trial Collaborative Group. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. *N Engl J Med* 2013; 368: 128–37.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Incidence of adverse effects. After the introduction of levonorgestrel in a subdermal implant formulation in February 1991, the US FDA had received about 5800 reports of adverse effects as of December 1993 (out of an estimated 891 000 implants distributed).[1] Serious adverse effects associated with the implant included 24 cases of infection related to insertion of the implant, 15 cases of stroke and 39 of benign intracranial hypertension, 3 cases of thrombocytopenic purpura and 6 of thrombocytopenia (1 fatal). None of the reporting rates for these disorders exceeded the expected rate in this population. In a 5-year cohort study[2] of more than 16 000 women who received either a levonorgestrel implant or an IUD (not progestogen-releasing), or underwent sterilisation, there was no significant risk of major morbidity associated with the implant, although there were moderately elevated risks of gallbladder disease and raised blood pressure in current users.

1. Wysowski DK, Green L. Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. *Obstet Gynecol* 1995; 85: 538–42.
2. Meirik O, *et al.* Safety and efficacy of levonorgestrel implant, intrauterine device, and sterilization. *Obstet Gynecol* 2001; 97: 539–47.

Benign intracranial hypertension. Intracranial hypertension, presenting as headaches, vomiting, and visual obscuration associated with florid bilateral papilloedema developed in 2 patients 4 to 5 months after subdermal implantation of levonorgestrel.[1] Despite a further 56 cases reported to various drug monitoring centres, and 70 cases known to the manufacturers,[2] it remained unclear whether the drug actually caused intracranial hypertension, but removal of implants was recommended in patients in whom intracranial pressure increased.

1. Alder JB, *et al.* Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 1995; 332: 1720–1.
2. Weber ME, *et al.* Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 1995; 332: 1721.

Breast feeding. Levonorgestrel was detected in breast milk and the circulation of breast-fed infants during the use of either a levonorgestrel IUD, subcutaneous implant, or progestogen-only oral contraceptive.[1] A review[2] of studies of a levonorgestrel implant used during lactation concluded that it did not adversely affect the duration of lactation, infant growth or development. Further studies of a levonorgestrel IUD[3] and implant[4] also found no adverse effect on lactation or infant growth. The implant study[4] did find an increased incidence of mild respiratory, skin, and eye diseases in infants in the first year of life, but the possibility of bias or chance could not be excluded. The American Academy of Pediatrics considers that levonorgestrel is usually compatible with breast feeding.[5] Progestogen-only contraceptives should not be started until several weeks after birth if the woman is breast feeding (see Breast Feeding under Hormonal Contraceptives, p. 2241.1).

In a pharmacokinetic study[6] using a single oral dose of levonorgestrel 1.5 mg, the drug concentration peaked between 2 and 4 hours in breast milk and then fell rapidly. The authors suggested that breast-feeding women who are given this dose of levonorgestrel for emergency contraception should be advised to breast feed immediately before the dose, then discard milk for at least 8 hours but not more than 24 hours.

1. Shikary ZK, *et al.* Transfer of levonorgestrel (LNG) administered through different drug delivery systems from the maternal circulation into the newborn infant's circulation via breast milk. *Contraception* 1987; 35: 477–86.
2. Díaz S. Contraceptive implants and lactation. *Contraception* 2002; 65: 39–46.
3. Shaamash AH, *et al.* A comparative study of the levonorgestrel-releasing intrauterine system Mirena versus the copper T380A intrauterine device during lactation: breast-feeding performance, infant growth and infant development. *Contraception* 2005; 72: 346–51.
4. Schlappacasse V, *et al.* Health and growth of infants breastfed by Norplant contraceptive implants users: a six-year follow-up study. *Contraception* 2002; 66: 57–65.
5. 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 27/06/08)

6. Gainer E, *et al.* Levonorgestrel pharmacokinetics in plasma and milk of lactating women who take 1.5 mg for emergency contraception. *Hum Reprod* 2007; 22: 1578–84.

Effects on the blood. Studies[1-3] of women who had been given different levonorgestrel subcutaneous implants found that over 5 years there were various changes in blood clotting factors, fibrinolytic activity, and platelet number and aggregation, some of which persisted even 6 months after removal of the implants. However, these haemostatic changes did not result in activation of the coagulation system or a state of hypercoagulation.

1. Singh K, *et al.* Evaluation of hemostatic function following Norplant implant removal. *Adv Contracept* 1993; 9: 49–58.
2. Singh K, *et al.* Evaluation of hemostatic function following Norplant-2 rods removal. *Adv Contracept* 1993; 9: 241–50.
3. Koh SCL, *et al.* A prospective study on the effects of reformulated 2-rod Norplant implant on haemostasis after five years of use. *J Obstet Gynaecol Res* 1999; 25: 177–83.

Effects on carbohydrate metabolism. For a mention that levonorgestrel has been reported to be the most potent progestogen associated with hyperinsulinaemia when used as a combined oral contraceptive, see p. 2236.3.

Glucocorticoid effects. Reference to the minimal suppressive effect of subdermal levonorgestrel on adrenal function.[1]

1. Toppozada MK, *et al.* Effect of Norplant implants on the pituitary-adrenal axis function and reserve capacity. *Contraception* 1997; 55: 7–10.

Myasthenia gravis. Myasthenia gravis occurring after insertion of a levonorgestrel implant improved on removal of the implant.[1]

1. Brittain J, Lange LS. Myasthenia gravis and levonorgestrel implant. *Lancet* 1995; 346: 1556.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levonorgestrel and oestrogen combinations 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 04/10/11)

Pregnancy. Adverse effects in infants whose mothers had received oral contraceptives containing norgestrel during early pregnancy have included tracheo-oesophageal fistula in one infant[1] and inoperable hepatoblastoma in another.[2] However, many epidemiological studies have failed to show any association between fetal malformations and oral contraceptives, even when used inadvertently during pregnancy, see p. 2242.1.

1. Frost O. Tracheo-oesophageal fistula associated with hormonal contraception during pregnancy. *BMJ* 1976; 2: 978.
2. Otten J, *et al.* Hepatoblastoma in an infant after contraceptive intake during pregnancy. *N Engl J Med* 1977; 297: 222.

Venous thromboembolism. For mention that levonorgestrel-containing combined oral contraceptives appeared to be associated with a lower incidence of venous thromboembolism than desogestrel- or gestodene-containing preparations, see p. 2238.1. See also Effects on the Blood, above.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

Levonorgestrel is rapidly and almost completely absorbed after an oral dose, and undergoes little first-pass hepatic metabolism. It is highly bound to plasma proteins; 42 to 68% to sex hormone binding globulin and 30 to 56% to albumin. The proportion bound to sex hormone binding globulin is higher when it is given with an oestrogen. Levonorgestrel and norgestrel are metabolised in the liver to sulfate and glucuronide conjugates, which are excreted in the urine and to a lesser extent in the faeces. Levonorgestrel is distributed into breast milk.

References.
1. Fotherby K. Levonorgestrel: clinical pharmacokinetics. *Clin Pharmacokinet* 1995; 28: 203–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Marplan; Microlut; Mirena; Norgestrel Continuo; Norgestrel Max; Ovulol; Postinor-2; Preventor; Secufem; Segurite; *Austral.*: Levonelle; Microlut; Microval†; Mirena; Norlevo; Postinor; *Austria*: Mirena; Postinor; Vikela; *Belg.*: Microlut; Mirena; Norlevo; Postinor; *Braz.*: Dia D; Minipil-2 Post; Minipil; Mirena; Neodia; Nortrel†; Pilem; Poslov; Postinor Uno; Postinor-2; Pozato; Previdez-2; Prevyol; *Canad.*: Mirena; Norlevo; Plan B; *Chile*: Microval; Mirena; Tace; *China*: An Ting (安婷); Escapelle (爱乐保)†; Hui Ting (惠婷); Mirena (曼月乐); Postinor (保仕婷); Yu Ting (毓婷); *Cz.*: Escapelle; Mirena; Postinor; *Denm.*: Mirena; NorLevo; *Fin.*: Jadelle; Microluton; Mirena; Norlevo; *Fr.*: Microval; Mirena; Norlevo; *Ger.*: 28 mini; Duofem†; Levogynon†; Microlut; Mirena; PiDaNa; unofem†; *Gr.*: Mirena; Norlevo; Postinor; *Hong Kong*: Escapelle; Mirena; Pill 72; Postinor-2; *Hung.*: Escapelle; Mirena; Rigesoft; *India*: Ecee; G-Pill; I-Pill; MPill; Nofear-72; Norlevo; Oh God; Pill 72; *Indon.*: Microlut; Mirena; Norplant†; Postinor-2; *Irl.*: Levonelle; Microval; Mirena; Norlevo; *Israel*: Afterday; Microlut; Mirena; Norlevo; Postinor; *Ital.*: Levonelle; Mirena; Norlevo; *Jpn*: NorLevo; *Malaysia*: Escapelle; Madonna; Me; Mirena; Postinor; *Mex.*: Alterna; Ceciora T; Dreams; Glanique; Hispatrel†; Ladiades; Microlut; Mirena; Post-Day; Postinor-2; Silogin; *Neth.*: Jadelle†; Mirena; Norlevo; Postinor; Vikela; *Norw.*: Jadelle†; Mirena; Norlevo; Postinor; *NZ*: Jadelle; Levonelle; Microlut; Mirena; Postinor; *Philipp.*: Mirena; *Pol.*: Escapelle; Mirena; Postinor-Duo†; *Port.*: Jadelle; Levonelle†; Mirena; Norlevo; Postinor; *Rus.*: Escapelle (Эскапел); Microlut (Микролют); Mirena (Мирена); Postinor (Постинор); *S.Afr.*: Escapelle; Microval; Mirena; Norlevo; *Singapore*: Estinor; Mirena; Postinor; *Spain*: Jadelle†; Mirena; Norlevo; Postinor; *Swed.*: Jadelle†; Levonova†; Mirena; NorLevo; Postinor; *Switz.*: Mirena; NorLevo; *Thai.*: Hyan; Jadelle: Madonna; Mirena; Norplant; Postinor; *Turk.*: Mirena; Norlevo; *UK*: Levonelle; Mirena; Norgeston; Postinor-2; Upostelle; *Ukr.*: Escapelle (Эскапел); Mirena (Мирена); Postinor (Постинор); *USA*: Mirena; My Way; Next Choice; Plan B; Skyla; *Venez.*: Jadelle; Microval; Mirena; Norlevo; Postinor-2.

Multi-ingredient Preparations. *Arg.*: Afrodita; Anubis; April; Ciclocur; Cuarcic†; Dos Dias N; Elektra; Evelea; Femexin; Loette; Microfem; Microgynon; Microvlar; Miranova; Neogynon; Nordette; Norfen; Norgestrel Cex; Norgestrel Minor; Norgestrel Plus; Tridestan N; Trinordiol; Triquilar; *Austral.*: Levlen ED; Loette; Logynon ED; Microgynon; Microlevlen ED; Monofeme; Nordette; Sequilar ED†; Trifeme; Triphasil; Triquilar; *Austria*: FemSeven Combi; Leonore; Loette; Madonella; Microgynon; Ovranette; Sequilar†; Trigynon†; Trinordiol; Xyliette; *Belg.*: Cyclocur; Eleonor; Feminova Plus; Lowette; Microgynon; Nora-30; Stediril 30; Trigynon; Trinordiol; *Braz.*: Anfertil; Ciclo; Ciclofemme; Cicloprimogyna; Concepnor; Evanor; Gesterlan; Level; Levordiol; Lindisc Duo; Lovelle; Microvlar; Miranova; Neovlar; Nocidin; Nordette; Normamor; Trinordiol; Triquilar; *Canad.*: Alesse; Aviane; Climara Pro; Min-Ovral; Ovral; Portia; Seasonale; Seasonique; Triquilar; *Chile*: Alesse†; Anovulatorio Micro-Dosis; Anulette; Fem 7 Combi; Femitres; Innova Cd; Microgynon; Miranova; Modutrol†; Nordette; Nordiol; Norvetal; Progyluton; Trinordiol; Triquilar; Trolit; *China*: Compound Norgestrel (复方炔诺孕酮); Duorina (多日纳); Triquilar (特居乐); Yueketing (悦可婷); *Cz.*: Gravistat; Klimonorm; Loette; Microgynon; Minisiston; Tri-Regol; Trinordiol†; Triquilar; *Denm.*: Femicept; Loette; Malonetta; Microgyn; Neogynon†; Nuvelle†; Rigevidon; Tercette; Triafem; Trimineta; Trinordiol†; Triquilar; Triregol: *Fin.*: Cyclabil†; FemSeven Combi†; Laurette; Microgynon; Miranova; Trikvilar; *Fr.*: Adepal; Amarance; Daily; Evanecia; Lovavulo; Ludeal; Minidril; Pacilla; Stediril; Trinordiol; *Ger.*: Asumate; Cyclo-Progynova N; CycloOstrogynal; Evalvna; Fem 7 Combi; Fem 7 Conti; Femigoa; Femigyne; Femranette mikro†; Gravistat; illina†; Klimonorm; Leios; Leona; Liana; Microgynon; Minisiston; Miranova; MonoStep; NovaStep; Ostronara; Triette†; Trigoa; Triquilar; Trisiston; Wellnara; *Gr.*: Cyclacur; Loette; Microgynon; Neogynon; Nordette; Nordiol; Nuvelle; Ovral; Trinordiol; Triquilar; *Hong Kong*: Eugynon†; Loette; Microgynon; Nordette; Rigevidon; Tri-Regol; *Hung.*: Anteovin†; FemSeven Combi†; Klimonorm; Loette†; Ovidon†; Rigevidon; Tri-Regol; Trinordiol†; Triquilar†; *India*: Choice; Combee; Dear-21; Divacon; Duoluton-L; Ergest; Loette; Ovilow; Ovimed; Ovipanz-I; Ovral; Triquilar; *Indon.*: Cyclo-Progynova; Microdiol; Microgynon; Pil Keluarga Berencana†; Planak; Trinordiol†; Triquilar; *Irl.*: FemSeven Conti; FemSeven Sequi†; Leonore; Logynon; Microlite; Ovogrel†; Ovran; Ovranette; Prempak-C; Rigevidon; Trinordiol; Vonodiol; *Israel*: Microgynon; Nordette; Progyluton; Seasonique; *Ital.*: Combiseven; Egogyn; Femity; Loette; Microgynon; Miranova; Novogyn; *Jpn*: Ange; *Malaysia*: Loette; Microgynon 30; Nordette; Oralcon; Progyluton; Rigevidon; Trigestrel; Trinordiol; *Mex.*: Alesse; Esdegen; Femexin; Letinnov; Microgynon; Neogynon; Nordet; Nordiol†; Ovral; Progyluton; Trinordiol; Triquilar; *Mon.*: FemseptCombi; Femseptevo; Leeloo; *Neth.*: Alesse†; Cyclocur†; Fem 7 Sequi†; Logynon†; Lovette; Microgynon; Miranova; Oralcon; Stediril; Trigynon; Trinordiol; *Norw.*: Loette; Microgynon; Oralcon; *NZ*: Levlen ED; Loette; Microgynon; Monofeme; Nordette; Nuvelle; *Roxanne*: Trifeme; Triphasil; Triquilar; *Philipp.*: Azul; Blush; Charlize; Femenal†; Femme; Lady; Logynon; Microgynon†; Nordette; Nordiol; Norfem; Rigevidon; Safe Pill; Seif; Trinordiol; Trust Pill; *Pol.*: Anteovin†; Cyclo-Progynova; Fem 7 Combi; Gravistat†; Klimonorm; Microgynon; Minisiston†; Rigevidon; Stediril; Tri-Regol; Trinordiol; Triquilar; Trisiston; *Port.*: Femsete Combi; Femsete Evo; Microginon; Miranova; Nuvelle; Progyluton; Tetragynon; Trinordiol; Triquilar†; *Rus.*: Anteovin (Антеовин)†; Cyclo-Progynova (Цикло-прогинова); Klimonorm (Климонорм); Microgynon (Микрогинон); Minisiston (Минизистон); Ovidon (Овидон)†; Rigevidon (Ригевидон); Tri-Regol (Три-Регол); Triquilar (Трикивлар); Trisiston (Трисистон); *S.Afr.*: Biphasil; E-Gen-C; Loette†; Logynon ED; Miranova†; Nordette; Nordiol; Ovral; Postoval; Triphasil; *Singapore*: Loette†; Microgynon; Nordette†; Prempak-C†; Progyluton; Trinordiol†; *Spain*: Levobel; Loette; Microgynon; Neogynona; Nuvelle†; Ovopiex; Progyluton; Triagynon; Triciclor; *Swed.*: Abelonelle; Neovletta; Prionelle; Trinordiol; Trionetta; Triregol; *Switz.*: Cyclacur; Elyfem; Levomin; Microgynon; Miranova; Ologyn; *Thai.*: Anna; Cyclo-Progynova; Dior; Jeny-FMP; Klimonorm†; Manodiol; Microgest†; Microgynon; Microlenyn; Nordette; Oralcon-F; R-Den; Riget†; Rigevidon; Trigestrel; Triquilar; *Turk.*: Cyclo-Progynova; Lo-Ovral; Microgynon; Miranova; Preven; Triquilar†; *UK*: Cyclo-Progynova 1 mg; Cyclo-Progynova 2 mg; FemSeven Conti; FemSeven Sequi; Levest; Logynon; Microgynon 30; Nuvelle†; Ovran 30; Ovranette; Prempak-C; Rigevidon; Triregol; *Ukr.*: Klimonorm (Климонорм); Microgynon (Микрогинон)†; Ovidon (Овидон)†; Rigevidon (Ригевидон); Tri-Regol (Три-Регол); Triquilar (Трикивлар); *USA*: Alesse†; Altavera; Amethia; Aviane; Camrese; Chateal; ClimaraPro; Cryselle; Daysee; Enpresse; Falmina; Jolessa; Kurvelo; Lessina; Levora; Lo/Ovral; LoSeasonique; Lutera; Lybrel; Marlissa; Myzilra; Nordette; Ovral†; Portia; Quartette; Quasense; Seasomale; Seasonique; Sronyx; Triphasil†; Trivora; *Venez.*: Alesse; Minigynon; Neogynon; Nordette; Nordiol; Ovral; Progyluton; Rigevidon; Tri-Regol; Trinordiol; Triquilar.

Pharmacopoeial Preparations

BP 2014: Levonorgestrel and Ethinylestradiol Tablets; Levonorgestrel Tablets; Norgestrel Tablets;
USP 36: Levonorgestrel and Ethinyl Estradiol Tablets; Norgestrel and Ethinyl Estradiol Tablets; Norgestrel Tablets.

Norgestrienone *(rINN)*

Norgestrienona; Norgestrienone; Norgestrienonum; Норгестриенон.

17β-Hydroxy-19-nor-17α-pregna-4,9,11-trien-20-yn-3-one.

$C_{20}H_{22}O_2$=294.4

CAS — 848-21-5.

ATC — G03AC07.

ATC Vet — QG03AC07.

UNII — 89386PYU9O.

Profile

Norgestrienone is a progestogen (see Progesterone, p. 2300.2) structurally related to norethisterone. It is used as a progestogen-only oral contraceptive (see p. 2231.3) in a dose of 350 micrograms daily. Norgestrienone has also been used with an oestrogen in combined oral contraceptives.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Ogyline†.

Normethandrone ⊗

Methylestrenolone; Methylestrenolonum; 17α-Methyl-19-nortestosterone; Methylnortestosterone; Metylostrenolon; Metyyliestrenoloni; Normethandrolone; NSC-10039; Норметандрон.

17β-Hydroxy-17α-methylestr-4-en-3-one.

$C_{19}H_{28}O_2$=288.4

CAS — 514-61-4.

ATC — G03DC31.

ATC Vet — QG03DC31.

UNII — 743F1Z557A.

Profile

Normethandrone is a progestogen that also has androgenic and anabolic properties. It has been given orally with an oestrogen for the treatment of amenorrhoea and menopausal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Indon.*: Mediol†; Renodiol; *Venez.*: Ginecosid.

Ormeloxifene *(rINN)* ⊗

Centchroman; Orméloxifène; Ormeloxifeno; Ormeloxifenum; Ормелоксифен.

trans-1-{2-[4-(3,4-Dihydro-7-methoxy-2,2-dimethyl-3-phenyl-2*H*-1-benzopyran-4-yl)phenoxy]ethyl}pyrrolidine.

$C_{30}H_{35}NO_3$=457.6

CAS — 31477-60-8.

ATC — G03XC04.

ATC Vet — QG03XC04.

UNII — 44AXY5VE90.

Profile

Ormeloxifene is a selective oestrogen receptor modulator with anti-oestrogenic actions and weak oestrogenic activity. It is used as an oral contraceptive (p. 2232.3), at a starting dose of 30 mg twice each week for 12 weeks, and followed by 30 mg once weekly thereafter. In the management of dysfunctional uterine bleeding (see Menorrhagia, p. 2300.3), 60 mg is given twice each week for 12 weeks,

then once weekly for up to 12 weeks. Ormeloxifene has been investigated in the management of benign breast diseases such as mastalgia. The *l*-isomer, levormeloxifene, which has oestrogenic effects, has been investigated in the management of postmenopausal osteoporosis, but development appears to have been discontinued because of adverse effects.

References.
1. Kamboj VP, *et al.* New products: centchroman. *Drugs Today* 1992; **28**: 227–32.
2. Gupta RC, *et al.* Centchroman: a new non-steroidal oral contraceptive in human milk. *Contraception* 1995; **52**: 301–5.
3. Lal J, *et al.* Pharmacokinetics of centchroman in healthy female subjects after oral administration. *Contraception* 1995; **52**: 297–300.
4. Lal J, *et al.* Optimization of contraceptive dosage regimen of centchroman. *Contraception* 2001; **63**: 47–51.
5. Alexandersen P, *et al.* Efficacy of levormeloxifene in the prevention of postmenopausal bone loss and on the lipid profile compared to low dose hormone replacement therapy. *J Clin Endocrinol Metab* 2001; **86**: 755–60.
6. Skrumsager BK, *et al.* Levormeloxifene: safety, pharmacodynamics and pharmacokinetics in healthy postmenopausal women following single and multiple doses of a new selective oestrogen receptor modulator. *Br J Clin Pharmacol* 2002; **53**: 284–95.
7. Ravn P, *et al.* What can be learned from the levormeloxifene experience? *Acta Obstet Gynecol Scand* 2006; **85**: 135–42.
8. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. *World J Surg* 2007; **31**: 1178–84.
9. Kriplani A, *et al.* Efficacy and safety of ormeloxifene in management of menorrhagia: a pilot study. *J Obstet Gynaecol Res* 2009; **35**: 746–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Centron†.

Ospemifene *(BAN, USAN, rINN)* ⊗

Fc-1271; FC-1271a; Ospémifène; Ospemifeno; Ospemifenum; Оспемифен.

2-[*p*-[(*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy]ethanol.

$C_{24}H_{23}ClO_2$=378.9

CAS — 128607-22-7.

UNII — B0P231ILBK.

NOTE. The name Ophena has been used as a trade mark for ospemifene.

Uses and Administration

Ospemifene is a selective oestrogen receptor modulator that appears to have oestrogen agonist or antagonist effects depending on tissue type. It is used in the treatment of dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The usual oral dose is 60 mg daily with food. It is also under investigation in the management of postmenopausal osteoporosis.

References.
1. Gennari L, *et al.* Ospemifene use in postmenopausal women. *Expert Opin Invest Drugs* 2009; **18**: 839–49.
2. McCall JL, DeGregorio MW. Pharmacologic evaluation of ospemifene. *Expert Opin Drug Metab Toxicol* 2010; **6**: 773–9.

Adverse Effects

The most common adverse effects of ospemifene are hot flushes, muscle spasm, hyperhidrosis, and vaginal discharge. Arterial and venous thromboembolic events, including thromboembolic stroke and deep-vein thrombosis, and haemorrhagic stroke have also been reported.

Precautions

Ospemifene should be avoided in women with active venous or arterial thromboembolism, or a history of thromboembolic disorders. It should be stopped at least 4 to 6 weeks before surgery that is associated with increased risk of thromboembolism. Ospemifene should be used with caution in women with risk factors for venous thromboembolism or for stroke. Ospemifene should not be used in patients with known or suspected oestrogen-dependent malignancy or undiagnosed uterine bleeding. It has not been studied in patients with severe hepatic impairment.

Ospemifene had adverse effects in *animal* teratogenicity studies and should not be used in women who are or may become pregnant.

Interactions

Ospemifene is mainly metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9; CYP2C19 and other pathways may also contribute. Interactions may occur with other drugs that inhibit or induce these enzymes. Plasma concentrations of ospemifene were reduced by the hepatic enzyme inducer rifampicin; increased plasma concentrations occurred with the enzyme inhibitor fluconazole.

Pharmacokinetics

Following oral dosing the peak median serum concentration of ospemifene is reached at about 2 hours. Steady-state concentrations are reached after about 9 days. Ospemifene is highly bound to serum proteins (more than 99%). It undergoes metabolism mainly by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19 and has an apparent terminal half-life of about 26 hours. About 75% of a dose of ospemifene is excreted in the faeces and 7% in the urine. Less than 0.2% is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Osphena.

Ovary Extracts

Extractos de ovario; Ovarian Extracts.

Profile

Ovary extracts of animal origin (usually porcine or bovine) have been used for a variety of disorders including gynaecological and menopausal disorders. They have often been used in preparations containing other mammalian tissue extracts or herbal medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Fr.*: Amphosca Ovarine; *Ger.*: Glandulae-F-Gastreu R20; Neydin-F†; NeyGeront Vitalkapseln A; *Neth.*: Chavita 1; Emvita 2; Emvita 3; Emvita 4.

Oxandrolone *(BAN, USAN, rINN)* ⊗

NSC-67068; Oxandrolona; Oxandrolonum; SC-11585; Оксандролон.

17β-Hydroxy-17α-methyl-2-oxa-5α-androstan-3-one.

$C_{19}H_{30}O_3$=306.4

CAS — 53-39-4.

ATC — A14AA08.

ATC Vet — QA14AA08.

UNII — 7H6TM3CT4L.

Pharmacopoeias. In *US*.

USP 36: (Oxandrolone). A white odourless crystalline powder. Soluble 1 in 5200 of water, 1 in 57 of alcohol, 1 in 69 of acetone, 1 in less than 5 of chloroform, and 1 in 860 of ether. Protect from light.

Uses and Administration

Oxandrolone has anabolic and androgenic properties (see Testosterone, p. 2305.2) and is given as adjunctive therapy to promote weight gain in oral doses of 2.5 to 20 mg daily in 2 to 4 divided doses. Treatment is usually given as a course of 2 to 4 weeks, which may be repeated intermittently as required. Elderly patients may be more susceptible to the adverse effects of oxandrolone, and a dose of up to 5 mg twice daily is recommended. See below for doses of oxandrolone used in children.

Administration in children. Oxandrolone has been given to children as adjunctive therapy to promote weight gain in oral doses of up to 100 micrograms/kg daily in 2 to 4 divided doses. Treatment is usually given as a course of 2 to 4 weeks, which may be repeated intermittently as required.

For the promotion of growth in boys with constitutional delay of growth and puberty, and in girls with Turner's syndrome, usual oral daily doses of 100 micrograms/kg have been used. Treatment may be given for up to a year, but bone age must be assessed during therapy to avoid the risk of premature epiphyseal closure (see also Growth Retardation, below).

Burns. For references to the use of oxandrolone in burn injuries see Cachexia, below.

Cachexia. Oxandrolone has been used for its protein anabolic effect in conditions associated with cachexia (p. 2289.3) or wasting,[1] including alcoholic hepatitis, burn injury,[2,3] HIV-infection, and muscular dystrophy (p. 1608.1).

1. Orr R, Singh MF. The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders: review of efficacy and safety. *Drugs* 2004; **64**: 725–50.
2. Miller JT, Btaiche IF. Oxandrolone in pediatric patients with severe thermal burn injury. *Ann Pharmacother* 2008; **42**: 1310–15.
3. Miller JT, Btaiche IF. Oxandrolone treatment in adults with severe thermal injury. *Pharmacotherapy* 2009; **29**: 213–26.

Growth retardation. A beneficial effect of oxandrolone on growth rate in *boys* with constitutional delay of growth and puberty (p. 2252.1) has been shown in various studies,[1-6] two of which[2,5] were placebo-controlled. Doses used have included 1.25 or 2.5 mg daily[1-3] and 50 or 100 micrograms/kg daily,[4-6] generally for 3 to 12 months. Although a slight advance in bone age has been noted,[1,4,5] final predicted height[5] and actual adult height[3] was not compromised by oxandrolone therapy. Oxandrolone did not affect the rate of pubertal progression and as the aim of such therapy is mainly to relieve psychosocial difficulties associated with short stature and sexual immaturity, it is not clear that it achieves this.[5]

Oxandrolone is also used for the promotion of growth in *girls* with Turner's syndrome (p. 2254.3), usually added to growth hormone therapy.[7-10]

1. Stanhope R, Brook CGD. Oxandrolone in low dose for constitutional delay of growth and puberty in boys. *Arch Dis Child* 1985; **60**: 379–81.
2. Stanhope R, *et al.* Double blind placebo controlled trial of low dose oxandrolone in the treatment of boys with constitutional delay of growth and puberty. *Arch Dis Child* 1988; **63**: 501–5.
3. Tse W-Y, *et al.* Long-term outcome of oxandrolone treatment in boys with constitutional delay of growth and puberty. *J Pediatr* 1990; **117**: 588–91.
4. Papadimitriou A, *et al.* Treatment of constitutional growth delay in prepubertal boys with a prolonged course of low dose oxandrolone. *Arch Dis Child* 1991; **66**: 841–3.
5. Wilson DM, *et al.* Oxandrolone therapy in constitutionally delayed growth and puberty. *Pediatrics* 1995; **96**: 1095–1100.
6. Lampit M, Hochberg Z. Androgen therapy in constitutional delay of growth. *Horm Res* 2003; **59**: 270–5.
7. Nilsson KO, *et al.* Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. *J Clin Endocrinol Metab* 1996; **81**: 635–40.
8. Ranke MB, *et al.* KIGS International Board. Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. *J Clin Endocrinol Metab* 2000; **85**: 4212–18.
9. Stahnke N, *et al.* Favorable final height outcome in girls with Ullrich-Turner syndrome treated with low-dose growth hormone together with oxandrolone despite starting treatment after 10 years of age. *J Pediatr Endocrinol Metab* 2002; **15**: 129–38.
10. Menke LA, *et al.* Efficacy and safety of oxandrolone in growth hormone-treated girls with Turner syndrome. *J Clin Endocrinol Metab* 2010; **95**: 1151–60.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3). As with other 17α-alkylated compounds, oxandrolone may cause hepatotoxicity, and liver function should be monitored. It should be avoided if hepatic impairment is severe.

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p. 2308.3).

Pharmacokinetics

Oxandrolone is rapidly absorbed from the gastrointestinal tract, and extensively bound to plasma proteins. It is excreted mainly in the urine as unchanged oxandrolone and some metabolites, with an elimination half-life of about 9 to 10 hours. A small amount is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Oxandrin†; *Mex.*: Xtendrol; *USA*: Oxandrin.

Pharmacopoeial Preparations

USP 36: Oxandrolone Tablets.

Oxymetholone *(BAN, USAN, rINN)* ⊗

Cl-406; HMD; Oksimetolon; Oksimetoloni; Oximetolon; Oximetolona; Oxymétholone; Oxymetholonum; Оксиметолон.

17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one.

$C_{21}H_{32}O_3$=332.5

CAS — 434-07-1.

ATC — A14AA05.

ATC Vet — QA14AA05.

UNII — L76T0ZCA8K.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Oxymetholone). A white to creamy-white, odourless or almost odourless, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform; slightly soluble in ether. Protect from light. Avoid contact with ferrous metals.

USP 36: (Oxymetholone). A white to creamy-white, odourless crystalline powder. Practically insoluble in water; soluble 1 in 40 of alcohol, 1 in 5 of chloroform, 1 in 82 of ether, and 1 in 14 of dioxan.

Uses and Administration

Oxymetholone has anabolic and androgenic properties (see Testosterone, p. 2305.2). It has been used mainly in the treatment of anaemias such as aplastic anaemia at a usual oral dose of 1 to 5 mg/kg daily. Treatment for 3 to 6 months has been suggested, with the drug either withdrawn

gradually on remission or reduced to an appropriate maintenance dose.

Reviews.

1. Pavlatos AM, *et al.* Review of oxymetholone: a 17α-alkylated anabolic-androgenic steroid. *Clin Ther* 2001; 23: 789–801.

Aplastic anaemia. There have been mixed results[1-5] with oxymetholone in the treatment of aplastic anaemia (p. 1121.3); generally, the response and survival rates have been disappointing. Although it was used extensively in the past, oxymetholone is now generally reserved for patients who have failed, or cannot tolerate, immunosuppressant therapy.

1. Davis S, Rubin AD. Treatment and prognosis in aplastic anaemia. *Lancet* 1972; i: 871–3.
2. Mir MA, Delamore IW. Oxymetholone in aplastic anaemia. *Postgrad Med J* 1974; 50: 166–71.
3. Camitta BM, *et al.* A prospective study of androgens and bone marrow transplantation for treatment of severe aplastic anemia. *Blood* 1979; 53: 504–14.
4. Mir MA, Geary CG. Aplastic anaemia: an analysis of 174 patients. *Postgrad Med J* 1980; 56: 322–9.
5. Webb DKH, *et al.* Acquired aplastic anaemia: still a serious disease. *Arch Dis Child* 1991; 66: 858–61.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

Liver disturbances and jaundice are common with normal doses and hepatic neoplasms have also been reported (see below). Liver function should be monitored during therapy. As with other 17α-alkylated compounds, oxymetholone should probably be avoided in patients with liver impairment, and certainly if this is severe.

Effects on carbohydrate metabolism. Pronounced hyperglucagonaemia developed in 6 patients receiving oxymetholone.[1]

1. Williams G, *et al.* Severe hyperglucagonaemia during treatment with oxymetholone. *BMJ* 1986; 292: 1637–8.

Effects on the liver. Peliosis hepatis[1-4] and various liver tumours[4-8] has been associated with oxymetholone use. A review[9] of reports of liver tumours associated with anabolic androgens found that oxymetholone was the androgen most often implicated, and that the majority of tumours were hepatocellular carcinomas.

1. Bagheri SA, Boyer JL. Peliosis hepatis associated with androgenic-anabolic steroid therapy: a severe form of hepatic injury. *Ann Intern Med* 1974; 81: 610–18.
2. McDonald EC, Speicher CE. Peliosis hepatis associated with administration of oxymetholone. *JAMA* 1978; 240: 243–4.
3. Hirose H, *et al.* Fatal splenic rupture in anabolic steroid-induced peliosis in a patient with myelodysplastic syndrome. *Br J Haematol* 1991; 78: 128–9.
4. Linares M, *et al.* Hepatocellular carcinoma and squamous cell carcinoma in a patent with Fanconi's anemia. *Ann Hematol* 1991; 63: 54–5.
5. Lesna M, *et al.* Liver nodules and androgens. *Lancet* 1976; i: 1124.
6. Mokrohisky ST, *et al.* Fulminant hepatic neoplasia after androgen therapy. *N Engl J Med* 1977; 296: 1411–12.
7. Kosaka A, *et al.* Hepatocellular carcinoma associated with anabolic steroid therapy: report of a case and review of the Japanese literature. *J Gastroenterol* 1996; 31: 450–4.
8. Nakao A, *et al.* Multiple hepatic adenomas caused by long-term administration of androgenic steroids for aplastic anemia in association with familial adenomatous polyposis. *J Gastroenterol* 2000; 35: 557–62.
9. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; 77: 257–67.

Effects on the nervous system. Toxic confusional state and choreiform movements developed in an elderly man given oxymetholone 200 to 300 mg daily.[1]

1. Tilzey A, *et al.* Toxic confusional state and choreiform movements after treatment with anabolic steroids. *BMJ* 1981; 283: 349–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Hemogenin; *India*: Adroyd; *Malaysia*: Oxylone; *Singapore*: Oxylone; *Thai.*: Androlic; *Turk.*: Anapolon; *USA*: Anadrol.

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

Polyestradiol Phosphate *(BAN, rINN)*

Fosfato de poliestradiol; Leo-114; Poliestradiol, fosfato de; Polyestradiol, Phosphate de; Polyestradiolfosfat; Polyestradioli Phosphas; Polyestradiolifosfaatti; Polyoestradiol Phosphate; Полиэстрадиола Фосфат.

A water-soluble polymeric ester of estradiol and phosphoric acid with a molecular weight of about 26 000.

CAS — 28014-46-2.
ATC — L02AA02.
ATC Vet — QL02AA02.
UNII — P1487?CDX2.

Uses and Administration

Polyestradiol phosphate is a polymer of estradiol (see p. 2271.1) that has a prolonged duration of action, and is used in the treatment of metastatic prostatic carcinoma (p. 712.3). It has been given by deep intramuscular injection in initial doses of 80 to 160 mg every 4 weeks for 2 to 3 months, reduced to 40 to 80 mg every 4 weeks for maintenance. Higher initial doses of up to 320 mg and maintenance doses of up to 240 mg have also been used.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). Pain may occur at the site of injection, and mepivacaine is included in some preparations to minimise this.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies polyestradiol phosphate 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 04/10/11)

Pharmacokinetics

After intramuscular injection polyestradiol phosphate is released slowly into the bloodstream where it is slowly metabolised to estradiol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Estradurin; *Belg.*: Estradurine†; *Denm.*: Estradurin; *Fin.*: Estradurin; *Norw.*: Estradurin†; *Rus.*: Estradurin (Эстрадурин); *Swed.*: Estradurin; *Switz.*: Estradurin; *Ukr.*: Estradurin (Эстрадурин)†.

Prasterone *(rINN)* ⊗

Dehydroandrosterone; Dehydroepiandrosteron; Dehydroepiandrosterone; Dehydroepiandrosteroni; Dehydroepiandrosteronum; Dehydroisoandrosterone; DHEA; GL-701; Prasterona; Prastérone; Prasteronum; Прастерон.

3β-Hydroxyandrost-5-en-17-one.

$C_{19}H_{28}O_2$=288.4

CAS — 53-43-0.
ATC — A14AA07.
ATC Vet — QA14AA07.
UNII — 459AG36T1B.

NOTE. The names Anastar, Aslera, Fidelin T, and Prestara have been used as trade marks for prasterone. The name Anastar has also been used for a proprietary preparation of anastrozole (p. 742.1). The name Aslera has also been used for proprietary preparations of serrapeptase (p. 2613.3).

Pharmacopoeias. In *Fr.*

Prasterone Enantate *(rINNM)* ⊗

Dehydroepiandrosterone Enanthate; EDHEA; Enantato de prasterona; Prasterona, enantato de; Prastérone, Enantate de; Prasterone Enanthate; Prasteroni Enantas; Прастерона Энантат.

3β-Hydroxyandrost-5-en-17-one heptanoate.

$C_{26}H_{40}O_3$=400.6

CAS — 23983-43-9.
ATC — A14AA07.
ATC Vet — QA14AA07.
UNII — 2W8I156T5L.

Prasterone Sodium Sulfate *(rINNM)* ⊗

Dehydroepiandrosterone Sulphate Sodium; DHA-S (prasterone sulfate); DHEAS (prasterone sulfate); PB-005; Prasterona, sulfato sódico de; Prasterone Sodium Sulphate; Prastérone, Sulfate Sodique de; Prasteroni Natrii Sulfas; Sulfato sódico de prasterona; Прастерона Натрия Сульфат.

3β-Hydroxyandrost-5-en-17-one hydrogen sulphate sodium.

$C_{19}H_{27}NaO_5S$=390.5

CAS — 651-48-9 (prasterone sulfate); 1099-87-2 (prasterone sodium sulfate).
ATC — A14AA07.
ATC Vet — QA14AA07.
UNII — E1CR8487EN.

NOTE. The names Aylistormer, Levospa, and Mylis have been used as trade marks for prasterone sodium sulfate.

Pharmacopoeias. *Chin.* includes the dihydrate.

Profile

Prasterone is a naturally occurring adrenal androgen that is a precursor of androgens and oestrogens. Prasterone enantate, in a dose of 200 mg every 4 weeks, is given by intramuscular depot injection with estradiol valerate as menopausal HRT (p. 2244.2). The sodium sulfate has been given for cervical ripening. Prasterone is also being investigated in adrenal insufficiency and in SLE, and the sodium sulfate has been investigated for the treatment of burns and acute asthma.

General reviews.

1. Kroboth PD, *et al.* DHEA and DHEA-S: a review. *J Clin Pharmacol* 1999; 39: 327–48.
2. Pepping J. DHEA: dehydroepiandrosterone. *Am J Health-Syst Pharm* 2000; 57: 2048–56.
3. Cameron DR, Braunstein GD. The use of dehydroepiandrosterone therapy in clinical practice. *Treat Endocrinol* 2005; 4: 95–114.

HIV infection and AIDS. Plasma concentrations of endogenous prasterone are reported to be abnormally low in patients with AIDS, and it has been suggested that use of prasterone might be of benefit; however, large controlled studies are lacking.[1] Small controlled studies have confirmed that oral use increases circulating concentrations of prasterone and its sulfated form, and have reported improvements in quality of life measures[2] and reductions in symptoms of mild depression,[3] but no beneficial antiviral or immunomodulatory effects.[4] Also, there were no significant changes in measures of serum lipids, insulin, growth hormone, or the overall function of the gonadal or hypothalamic-pituitary-adrenal axes.[5]

1. Centurelli MA, *et al.* The role of dehydroepiandrosterone in AIDS. *Ann Pharmacother* 1997; 31: 639–42.
2. Piketty C, *et al.* Double-blind placebo-controlled trial of oral dehydroepiandrosterone in patients with advanced HIV disease. *Clin Endocrinol (Oxf)* 2001; 55: 325–30.
3. Rabkin JG, *et al.* Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS. *Am J Psychiatry* 2006; 163: 59–66.
4. Abrams DI, *et al.* Dehydroepiandrosterone (DHEA) effects on HIV replication and host immunity: a randomized placebo-controlled study. *AIDS Res Hum Retroviruses* 2007; 23: 77–85.
5. Poretsky L, *et al.* Endocrine effects of oral dehydroepiandrosterone in men with HIV infection: a prospective, randomized, double-blind, placebo-controlled trial. *Metabolism* 2006; 55: 858–70.

Replacement therapy. There has been much speculation about the physiological role and importance of prasterone, which is the most abundant steroid hormone in the circulation. It is produced by the adrenal gland and is a precursor of androgens and oestrogens. Serum concentrations peak at about 20 years then gradually decline with age. Epidemiological and *animal* studies suggest that certain age-related diseases may be linked to this decline, including reduced immunocompetence, obesity, diabetes, and cancers.[1] It has been suggested, therefore, that replacement therapy with prasterone might alleviate some of the problems of ageing. Prasterone has been studied for its effect on cognition and memory, sexual function, insulin sensitivity, cardiovascular risk factors, muscle strength and body composition, bone loss, and immune function, but results have generally been conflicting,[1,2] and there is insufficient evidence of safety and efficacy to recommend such use. A systematic review[3] of studies in healthy adults taking prasterone supplementation found no support for an improvement in cognitive function. A review[4] of the use of prasterone as a 'food supplement' noted that although it was being taken in the belief that it could reverse some of the effects of ageing there was no good evidence of this. Various androgenic effects, including hirsutism and voice changes, have been reported in women taking prasterone and there is a theoretical possibility that it might promote growth of hormone-sensitive tumours in both sexes.[1,4]

Prasterone has also been studied as replacement therapy for patients with adrenal insufficiency, who have subnormal levels of prasterone. Such therapy, usually in oral doses of 50 mg daily, has been reported to raise serum levels of prasterone to normal, and improve measures of well-being, mood, and fatigue.[1,5-7] Others[8] have found no significant improvement in fatigue, cognitive function, or sexual function after 12 months of treatment, but did detect beneficial effects on bone mineral density in the femoral neck, lean body-mass, and some measures of psychological well-being. A systematic review[9] of its effects on quality of life in women with adrenal insufficiency concluded that there was insufficient evidence of benefit to recommend its use. There have been mixed results from studies of the effects of prasterone on carbohydrate metabolism with reports of either no effect[10,11] or increased insulin sensitivity.[12] Prasterone may have an unfavourable effect on the lipoprotein profile of hypoadrenal women.[13]

1. Dhatariya KK, Nair KS. Dehydroepiandrosterone: is there a role for replacement? *Mayo Clin Proc* 2003; 78: 1257–73.
2. GISEG (Italian Study Group on Geriatric Endocrinology). Consensus document on substitution therapy with DHEA in the elderly. *Aging Clin Exp Res* 2006; 18: 277–300. Also available at: http://www.kurtis.it/abs/index.cfm?id_articolo_numero=2297 (accessed 13/11/07)

3. Grimley Evans J, *et al.* Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 13/11/07).
4. Anonymous. Dehydroepiandrosterone (DHEA). *Med Lett Drugs Ther* 1996; 38: 91–2.
5. Arit W, *et al.* Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999; 341: 1013–20.
6. Hunt PJ, *et al.* Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab* 2000; 85: 4650–6.
7. Brooke AM, *et al.* Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. *J Clin Endocrinol Metab* 2006; 91: 3773–9.
8. Gurnell EM, *et al.* Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial. *J Clin Endocrinol Metab* 2008; 93: 400–409.
9. Alkatib AA, *et al.* A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. *J Clin Endocrinol Metab* 2009; 94: 3676–81.
10. Callies F, *et al.* Dehydroepiandrosterone replacement in women with adrenal insufficiency: effects on body composition, serum leptin, bone turnover, and exercise capacity. *J Clin Endocrinol Metab* 2001; 86: 1968–72.
11. Libè R, *et al.* Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism. *J Endocrinol Invest* 2004; 27: 736–41.
12. Dhatariya K, *et al.* Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. *Diabetes* 2005; 54: 765–9.
13. Srinivasan M, *et al.* Effect of dehydroepiandrosterone replacement on lipoprotein profile in hypoadrenal women. *J Clin Endocrinol Metab* 2009; 94: 761–4.

Systemic lupus erythematosus. In several small studies carried out by one group,[1-5] there was symptomatic improvement in SLE (p. 1613.3), and a reduction in corticosteroid dosage, in women who received oral prasterone 200 mg daily for several months. Although they considered that there was clear evidence of benefit,[6] larger studies[7-9] have produced more statistically ambiguous results. They suggested that prasterone might stabilise or improve disease, and reduce corticosteroid requirements and time to disease flare, but only in patients with active disease. Nested data from one of these studies[10] also showed that prasterone treatment for up to a year improved bone mineral density of the lumbar spine and hip. A larger study[11] of 155 women receiving chronic corticosteroid therapy was designed to confirm this effect on bone. The results were not statistically significant in favour of prasterone in the first 6 placebo-controlled months. However, an open-label 1-year extension found a small increase in bone mineral density of the lumbar spine, and maintenance in density of the hip, in patients given prasterone 200 mg daily for 18 months; a lower dose of 100 mg daily was not protective. In a study[12] of lumbar spine bone mineral density in women with quiescent SLE, prasterone may have had a protective effect in postmenopausal women who were not otherwise treated with oestrogens or bisphosphonates, but there was no change in premenopausal women.

1. van Vollenhoven RF, *et al.* An open study of dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 1994; 37: 1305–10.
2. van Vollenhoven RF, *et al.* Dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 1995; 38: 1826–31.
3. van Vollenhoven RF, *et al.* Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months. *J Rheumatol* 1998; 25: 285–9.
4. Barry NN, *et al.* Dehydroepiandrosterone in systemic lupus erythematosus: relationship between dosage, serum levels, and clinical response. *J Rheumatol* 1998; 25: 2352–6.
5. van Vollenhoven RF, *et al.* A double-blind, placebo-controlled, clinical trial of dehydroepiandrosterone in severe systemic lupus erythematosus. *Lupus* 1999; 8: 181–7.
6. van Vollenhoven RF. Dehydroepiandrosterone in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000; 26: 349–62.
7. Petri MA, *et al.* Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2002; 46: 1820–9.
8. Chang D-M, *et al.* Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus. *Arthritis Rheum* 2002; 46: 2924–7.
9. Petri MA, *et al.* Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematosus: results of a multicenter randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004; 50: 2858–68.
10. Mease PJ, *et al.* Effects of prasterone on bone mineral density in women with systemic lupus erythematosus receiving chronic glucocorticoid therapy. *J Rheumatol* 2005; 32: 616–21.
11. Sánchez-Guerrero J, *et al.* Effects of prasterone on bone mineral density in women with active systemic lupus erythematosus receiving chronic glucocorticoid therapy. *J Rheumatol* 2008; 35: 1567–75.
12. Hartkamp A, *et al.* The effect of dehydroepiandrosterone on lumbar spine bone mineral density in patients with quiescent systemic lupus erythematosus. *Arthritis Rheum* 2004; 50: 3591–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Di Luo An (蒂洛安); *Mex.*: Biolaif; *Pol.*: Biosteron; BioStym Balance.

Multi-ingredient Preparations. *Arg.*: Dastonil; Gynodian Depot; Longevital; Supligol NF; *Austria*: Gynodian Depot; *Chile*: Gynodian Depot; *Cz.*: Gynodian Depot; *Ger.*: Gynodian Depot; *Ital.*: Gynodian Depot; *Mex.*: Binodian; Sten; *Pol.*: Gynodian Depot†; *Rus.*: Gynodian Depot (Гинодиан Депо)†; *Switz.*: Gynodian Depot; *Venez.*: Gynodian Depot.

Progesterone *(BAN, rINN)*

Corpus Luteum Hormone; Luteal Hormone; Luteine; Luteohormone; NSC-9704; Pregnenedione; Pregnenodiona; Progesteron; Progesterona; Progesteronas; Progestérone; Progesteroni; Progesteronum; Progestina; Progeszteron; Прогестерон.

Pregn-4-ene-3,20-dione.

$C_{21}H_{30}O_2$=314.5

CAS — 57-83-0.

ATC — G03DA04.

ATC Vet — QG03DA04.

UNII — 4G7DS2Q64Y.

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

Ph. Eur. 8: (Progesterone). A white or almost white crystalline powder or colourless crystals. It exhibits polymorphism. Practically insoluble in water; freely soluble in dehydrated alcohol; sparingly soluble in acetone and in fatty oils. Protect from light.

USP 36: (Progesterone). A white or creamy-white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in dioxan; sparingly soluble in vegetable oils. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Progesterone is a natural hormone whereas progestogens are synthetic compounds, derived from progesterone or 19-nortestosterone, with actions similar to those of progesterone (for further details, see p. 2231.1).

Progestogens derived from 19-nortestosterone are used as **hormonal contraceptives** (see p. 2231.3), either alone or combined with an oestrogen. The progesterone derivative medroxyprogesterone acetate is also used, and progesterone itself has been used.

Progestogens, and sometimes progesterone, are used with oestrogens for **menopausal HRT** (p. 2244.2) to reduce the increased risk of endometrial hyperplasia and carcinoma that occurs when long-term oestrogen therapy is unopposed.

Similarly, drugs with progestogenic actions may be used in **menstrual disorders** such as dysmenorrhoea (p. 8.2) and menorrhagia associated with dysfunctional uterine bleeding (below). Progestogens may also be used in the management of endometriosis (p. 2264.1). Although progestogens and progesterone have been used for the management of the premenstrual syndrome (p. 2301.2), such a practice is of debatable value.

Progestogens may be valuable in advanced **endometrial cancer** (p. 704.3) and have been tried in some other malignancies. The progestogens typically used for malignant disease include medroxyprogesterone acetate, megestrol, and norethisterone. Some progestogens such as megestrol and medroxyprogesterone are used for the **cachexia** or wasting associated with severe illness including cancer and AIDS (p. 2289.3).

Progestogens have been widely advocated for either the prevention of **recurrent miscarriage** or the treatment of threatened miscarriage (p. 2301.2). However, there is little evidence of any benefit from such a practice and the use of progestogens in early pregnancy is not now generally advised, with the exception of the use of progesterone or a progesterone derivative in women who are progesterone deficient (see also Precautions, p. 2301.3). Progesterone is, however, the preferred drug for luteal support in women undergoing **assisted reproductive techniques** such as IVF (see Infertility, p. 2253.1).

USES AND ADMINISTRATION OF PROGESTERONE. Progesterone is usually given as an oily intramuscular injection, a vaginal gel or pessaries, or as suppositories. Preparations containing micronised progesterone are also available for oral and vaginal use.

In dysfunctional uterine bleeding or amenorrhoea 5 to 10 mg daily of progesterone may be given by intramuscular injection for about 5 to 10 days until 2 days before the anticipated onset of menstruation. Alternatively, progesterone may be given for amenorrhoea as a vaginal gel at a usual dose of 45 mg on alternate days for up to 6 doses; the dose may be increased to 90 mg in those who do not respond to the lower dose. An oral dose of 400 mg given daily at bedtime for 10 days may also be used for amenorrhoea.

In women with a history of recurrent miscarriage and proven progesterone deficiency, twice weekly intramuscular injection (increased to daily if necessary) of 25 to 100 mg of progesterone, from about day 15 of the pregnancy until 8 to 16 weeks, has been used. The dose may be increased to 200 mg daily if necessary. Vaginal doses of micronised progesterone 200 to 400 mg daily, in 2 divided doses, have also been given until week 12 of pregnancy. A similar intramuscular schedule has been used for luteal support in IVF or gamete intra-fallopian transfer techniques with treatment beginning on the day of transfer of embryo or gametes. Alternatively, progesterone may be given vaginally in assisted reproduction, but doses can vary widely depending on the preparation. A vaginal gel may be given at a dose of 90 mg daily; it is given for 30 days if pregnancy occurs, and may be continued until there is placental autonomy (up to 10 to 12 weeks). A dose of 90 mg twice daily has been used in women with ovarian failure. A vaginal tablet containing micronised progesterone 100 mg may be given 2 or 3 times daily; treatment is started at oocyte retrieval and continued for up to 10 weeks. Some soft capsules containing micronised progesterone may also be suitable for intravaginal use in a dose of 400 to 600 mg daily, in 2 or 3 divided doses, from the day of gonadotrophin administration until week 12 of pregnancy.

Progesterone may be given vaginally or rectally in doses of 200 mg daily to 400 mg twice daily for the management of the premenstrual syndrome. Treatment usually starts on day 12 to 14 of the menstrual cycle and continues until the onset of menstruation. Similar vaginal or rectal doses have also been used in the treatment of puerperal (post-natal) depression.

Progesterone has been given as the progestogen component of menopausal HRT. Soft capsules containing micronised progesterone are available in some countries for oral use, given in a dose of 200 mg daily at bedtime for 12 to 14 days of each month. Alternatively, a dose of 100 mg daily may be given from day 1 to 25 of each cycle, resulting in less withdrawal bleeding.

A progesterone-releasing intra-uterine device has been used as a hormonal contraceptive; the device contained 38 mg of progesterone and was effective for up to 12 months. A vaginal ring device that releases 10 mg of progesterone daily is used in some countries for contraception in lactating women. The first ring is inserted 6 weeks after delivery, then replaced every 90 days.

Administration. Progesterone creams for *topical* application to the skin are promoted in some countries for the management of menopausal symptoms and conditions associated with progesterone deficiency. These are sometimes described as containing 'natural' progesterone or phytoprogesterone from plant sources. However, many of these products are available without prescription or medical consultation and there has been some concern about their safety and efficacy. Reviews[1,2] have found early studies reporting that absorption of progesterone from these creams was minimal. However, a later study[3] using liquid chromatography-tandem spectrometry of whole blood reported that steady-state progesterone exposure was similar for women given either oral micronised progesterone or topical cream.[3] The authors suggested that the differences between their results and previous studies were likely to have been caused by the use of different analytical techniques, and that women using these creams may in fact be exposed to higher systemic concentrations of progesterone than previously thought. Some proponents of topical progesterone therapy have questioned the importance of using serum concentrations as a marker for absorption. A review[4] concluded that available serum-progesterone concentrations probably remain low after topical use and that further studies on the pharmacokinetics of topical progesterone are needed. In terms of efficacy, several small controlled studies have not shown progesterone cream to be any better than placebo for the management of menopausal vasomotor symptoms or the prevention of bone loss, and mixed results have been reported regarding the prevention of endometrial proliferation associated with oestrogen therapy.[1,2,4]

1. Anonymous. Natural' progesterone creams for postmenopausal women. *Drug Ther Bull* 2001; 39: 10–11.
2. Wren BG. Transdermal progesterone creams for postmenopausal women: more hype than hope? *Med J Aust* 2005; 182: 237–9.
3. Hermann AC, *et al.* Over-the-counter progesterone cream produces significant drug exposure compared to a Food and Drug Administration-approved oral progesterone product. *J Clin Pharmacol* 2005; 45: 614–19.
4. Elshafie MAA, Ewies AAA. Transdermal natural progesterone cream for postmenopausal women: inconsistent data and complex pharmacokinetics. *J Obstet Gynaecol* 2007; 27: 655–9.

Menorrhagia. Menorrhagia, or excessive menstrual bleeding, is usually defined as a blood loss exceeding 80 mL per menstrual period,[1,2] compared with a normal loss of about 30 mL. However, many women consider losses below 80 mL to be excessive particularly if 'flooding' occurs. Although not life-threatening, menorrhagia can lead to iron deficiency anaemia and considerably impair quality of life. Menorrhagia may be associated with pelvic disorders such as fibroids or endometriosis, the use of copper IUDs, or some systemic disorders.[1-3] However, most commonly it is associated with dysfunctional uterine bleeding;[1] a term used to denote frequent, prolonged or heavy uterine

bleeding for which no specific cause is found (essential, idiopathic, or primary menorrhagia). Both ovulatory (regular) and anovulatory cycles may give rise to dysfunctional uterine bleeding.[2] In general, medical treatment is used initially in women with no underlying uterine abnormalities.[3] The most commonly used drugs are NSAIDs, tranexamic acid, combined oral contraceptives, and progestogens, and choice of therapy may be influenced by the contraceptive needs of the patient.[1-3] Surgery can be used if medical management is ineffective, and may be considered for first-line treatment in selected patients.[3]

NSAIDs such as mefenamic acid, ibuprofen, and naproxen have been widely used. They reduce menstrual blood loss by about 20 to 50%, and there does not seem to be evidence to suggest that one NSAID is more effective than another.[1] They are taken only during the menstrual phase, which reduces adverse effects, and probably improves patient compliance; they also have the benefit of relieving dysmenorrhoea (p. 8.2).[1] Systematic review[4] suggests that NSAIDs are less effective than tranexamic acid, danazol, and intra-uterine levonorgestrel in reducing bleeding. NSAIDs are considered a suitable option when hormonal therapy is not acceptable. They should be stopped if symptoms do not improve within three menstrual cycles, but can be used for as long as the patient finds them to be beneficial.[3]

Given during menstruation *tranexamic acid* reduces menstrual blood loss by about half;[1] the benefits of tranexamic therapy have been confirmed by systematic review.[5] Like NSAIDs, tranexamic acid is considered a suitable option when hormonal therapy is not acceptable. It should be stopped if symptoms do not improve within three menstrual cycles, but can be used for as long as the patient finds it to be beneficial.[3] *Etamsylate* has been used for menorrhagia, but it is less effective than NSAIDs and tranexamic acid, and is no longer recommended.[1,3]

In women who require contraception, a *combined oral contraceptive* appears to be effective,[1,3] although good evidence of this is actually lacking.[6] It has been suggested that extended-cycle regimens should be considered for women with menorrhagia, as there are fewer bleeding episodes per year of treatment.[2] Traditional therapy with *progestogens* such as norethisterone or medroxyprogesterone given during the luteal phase appears to be ineffective in women with normal ovulatory cycles,[1,3,7] although cyclical therapy may be of benefit in anovulatory patients as it imposes a cycle.[2] Progestogen therapy for 21 days of the cycle results in a significant reduction in menstrual blood loss,[1,3,7] but is associated with adverse effects that may limit its acceptability. Long-acting injectable progestogens, such as medroxyprogesterone acetate, reduce menstrual blood loss or induce amenorrhoea when they are used as contraceptives. They have therefore been used for menorrhagia, although specific studies for this indication are lacking.[1,3]

More recently, a contraceptive *levonorgestrel-containing IUD* has been shown to be very effective in reducing menstrual blood loss in menorrhagia.[1,2] UK guidelines[3] suggest that it should be considered first when either hormonal or non-hormonal treatment is acceptable and long-term use is anticipated, although comparative data are scanty.[8] There is also some evidence that it may be an effective alternative to surgery, but data from long-term follow-up are needed.[9] As there can be changes in bleeding pattern associated with this device, particularly in the first few cycles, use for at least 6 months is advised to enable full assessment of benefit.[3]

Danazol is also effective,[10] producing about a 50% reduction in menstrual blood loss,[1] but has significant adverse effects and treatment is usually limited to 3 to 6 months. *Gonadorelin analogues* are effective for menorrhagia associated with fibroids (p. 2281.2).[1] When used preoperatively for endometrial thinning, they produce more consistent results than danazol.[11] Gonadorelin analogues may therefore be considered before surgery or when other options for fibroids are contra-indicated, but 'add-back' hormone replacement is recommended for the management of adverse effects from oestrogen deficiency or if they are used for more than 6 months.[3]

In patients who fail to respond to drug treatment, or in whom such therapy is inappropriate, various *surgical options* exist. Conservative surgical techniques, where the endometrium is ablated or resected, are increasingly being used, and are an effective alternative to hysterectomy.[3,12] Hysterectomy is the ultimate therapy, but is associated with significant morbidity.

1. Roy SN, Bhattacharya S. Benefits and risks of pharmacological agents used for the treatment of menorrhagia. *Drug Safety* 2004; 27: 75–90.
2. Nelson AL, Teal SB. Medical therapies for chronic menorrhagia. *Obstet Gynecol Surv* 2007; 62: 272–81.
3. National Collaborating Centre for Women's and Children's Health/NICE. Heavy menstrual bleeding (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf (accessed 27/06/08)
4. Lethaby A, *et al.* Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/06/08).
5. Lethaby A, *et al.* Antifibrinolytics for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 27/06/08).
6. Farquhar C, Brown J. Oral contraceptive pill for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/11/09).
7. Lethaby A, *et al.* Cyclical progestogens for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).
8. Lethaby AE, *et al.* Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 27/06/08).
9. Marjoribanks J, *et al.* Surgery versus medical therapy for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 27/06/08).
10. Beaumont H, *et al.* Danazol for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
11. Sowter MC, *et al.* Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 27/06/08).
12. Lethaby A, *et al.* Endometrial resection/ablation techniques for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/11/09).

Miscarriage. Threatened miscarriage is a common complication of pregnancy that presents before 20 weeks of gestation as vaginal bleeding, with or without abdominal pain, while the cervix is closed and the fetus is viable. Endogenous progesterone is normally produced by the corpus luteum to maintain pregnancy, and low concentrations have been associated with pregnancy loss. Progestogen therapy has therefore been widely used in the treatment of threatened miscarriage,[1] but there is a paucity of clinical study data to support routine use.[2] Similarly, progestogens have been used prophylactically to prevent miscarriage, but studies have suffered from various limitations.[3] A systematic review[4] found no evidence to support routine use, but there was limited evidence to suggest that women with a history of recurrent miscarriage (3 or more consecutive miscarriages) might gain some benefit. The *BNF* advises that progestogen prophylaxis in women with a history of recurrent miscarriage is not recommended. (See also Pregnancy, p. 2302.1, for reports of hypospadias in the offspring of women given hormonal support therapy.)

1. Sotiriadis A, *et al.* Threatened miscarriage: evaluation and management. *BMJ* 2004; 329: 152–5.
2. Wahabi HA, *et al.* Progestogen for treating threatened miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
3. Walch KT, Huber JC. Progesterone for recurrent miscarriage: truth and deceptions. *Best Pract Res Clin Obstet Gynaecol* 2008; 22: 375–89.
4. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 27/06/08).

Premature labour. Recommendations have been made regarding progesterone therapy for the prevention of premature birth in women at risk of preterm delivery (see under Hydroxyprogesterone Caproate, p. 2285.1).

Premenstrual syndrome. Progestogen therapy was once popular for premenstrual syndrome, but beneficial responses have not been universally achieved and the theory that progesterone was necessary to correct a hormone imbalance is now losing ground (see p. 2272.3). Progesterone has been given orally, vaginally, and rectally, in continuous and luteal phase regimens. However, systematic reviews[1,2] have found no convincing evidence to support its use.

1. Wyatt K, *et al.* Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; 323: 776–80.
2. Ford O, *et al.* Progesterone for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 20/11/09).

Spinal cord and head injury. Progesterone is under investigation as a neuroprotectant in the treatment of traumatic brain injury.[1-3]

1. Wright DW, *et al.* Steady-state serum concentrations of progesterone following continuous intravenous infusion in patients with acute moderate to severe traumatic brain injury. *J Clin Pharmacol* 2005; 45: 640–8.
2. Wright DW, *et al.* ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. *Ann Emerg Med* 2007; 49: 391–402.
3. 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.

Adverse Effects

Progesterone and the progestogens may cause gastrointestinal disturbances, changes in appetite or weight, fluid retention, oedema, acne, chloasma (melasma), allergic skin rashes, urticaria, mental depression, breast changes including discomfort or occasionally gynaecomastia, changes in libido, hair loss, hirsutism, fatigue, drowsiness or insomnia, fever, headache, premenstrual syndrome-like symptoms, and altered menstrual cycles or irregular menstrual bleeding. Anaphylaxis or anaphylactoid reactions may occur rarely. Alterations in the serum lipid profile may occur, and rarely alterations in liver-function tests and jaundice. Pain, diarrhoea, and flatulence have followed rectal use. Injection-site reactions have followed parenteral use.

Adverse effects vary depending on the dose and type of progestogen. For example, androgenic effects such as acne and hirsutism are more likely to occur with nortestosterone derivatives such as norethisterone and norgestrel. These derivatives may also be more likely to adversely affect serum lipids. Conversely, adverse effects on serum lipids appear less likely with gestodene and desogestrel, but these 2 drugs have been associated with a higher incidence of thromboembolism than norethisterone and norgestrel when used in combined oral contraceptives (see p. 2238.1). High doses of progestogens such as those used in treating cancer have also been associated with thromboembolism. For a discussion of the effect of progestogens on the cardiovascular risk profile of menopausal HRT see p. 2248.2. Breakthrough uterine bleeding is more common with oral progestogen-only contraceptives than when progestogens are used for menstrual irregularities or as part of menopausal HRT.

Some progestogens when given during pregnancy have been reported to cause virilisation of a female fetus. This appears to have been associated with those progestogens with more pronounced androgenic activity such as norethisterone; the natural progestogenic hormone progesterone and its derivatives such as dydrogesterone and medroxyprogesterone do not appear to have been associated with such effects.

For the adverse effects of progestogens when administered either alone or with oestrogens as contraceptives, see p. 2233.3. For those of menopausal HRT, see p. 2246.3.

Carcinogenicity. In a cohort study[1] of women aged 40 to 64 years, the premenopausal use of oral progestogens alone, mainly for benign breast, uterine, and ovarian conditions, and irregular menstruation, was not associated with an increased risk of breast cancer. However, the data did suggest that there was an increased risk for current users of progestogens for longer than 4.5 years (relative risk 1.44, 95% confidence interval 1.03 to 2.00) compared with women who had never used progestogens. Limitations of this study included the lack of analysis of different progestogens or a record of the reasons for progestogen treatment.

1. Fabre A, *et al.* Oral progestagens before menopause and breast cancer risk. *Br J Cancer* 2007; 96: 841–4.

Effects on the skin. Auto-immune progesterone dermatitis includes reactions such as eczema, urticaria, and angioedema that usually begin 3 to 10 days before the onset of menstrual flow and end 1 to 2 days into menses, which correlates with raised endogenous progesterone concentrations during the luteal phase of the menstrual cycle. The onset of the condition can be as early as menarche, and many women have never been exposed to exogenous progesterone, but it has also occurred in women with a history of oral contraceptive use. Management has been based on the suppression of endogenous progesterone secretion and oral contraceptives are usually tried first, although they appear to have limited success possibly because of the progestogen component. Other drugs that have been used include corticosteroids, conjugated oestrogens, gonadorelin analogues, androgens, and tamoxifen, but all have significant adverse effects associated with long-term use. Bilateral oophorectomy has been used in severe cases, when drug therapy has been unsuccessful.[1]

A woman with a history of auto-immune progesterone dermatitis developed pruritic, pink, oedematous plaques and macules on the upper thighs, axillae, and buttocks after the use of vaginal progestogen gel during infertility treatment.[2] The reaction was managed with topical corticosteroids. In another woman, with a history of chronic urticaria exacerbated by progesterone, the use of progesterone and various other progestogens as a component of HRT after oophorectomy caused urticaria and angioedema.[3] Desensitisation using micronised progesterone was successful in this case.

1. Baptist AP, Baldwin JL. Autoimmune progesterone dermatitis in a patient with endometriosis: case report and review of the literature. *Clin Mol Allergy* 2004; 2: 10.
2. Jenkins J, *et al.* Autoimmune progesterone dermatitis associated with infertility treatment. *J Am Acad Dermatol* 2008; 58: 353–5.
3. Poole JA, Rosenwasser LJ. Chronic idiopathic urticaria exacerbated with progesterone therapy treated with a novel desensitization protocol. *J Allergy Clin Immunol* 2004; 114: 456–7.

Precautions

Progesterone and the progestogens should be used with caution in patients with hypertension, cardiac or renal impairment, asthma, epilepsy, and migraine, or other conditions which may be aggravated by fluid retention. Progestogens can decrease glucose tolerance and diabetic

The symbol † denotes a preparation no longer actively marketed

patients should be carefully monitored. They should also be used with care in persons with a history of depression. High doses should be used with caution in patients susceptible to thromboembolism.

Progesterone and the progestogens should not be given to patients with undiagnosed vaginal bleeding, nor to those with a history or current high risk of arterial disease and should generally be avoided in hepatic impairment, especially if severe. Unless progestogens are being used as part of the management of breast or genital-tract carcinoma they should not be given to patients with these conditions.

Although progestogens have been given as hormonal support during early pregnancy such use is not now generally advised. However, the use of a progesterone-type progestogen might still be considered for women who are progesterone-deficient. Such use may prevent spontaneous evacuation of a dead fetus, therefore careful monitoring of pregnancy is required. Progestogens should not be used diagnostically for pregnancy testing and should not be given in missed or incomplete abortion.

For precautions to be observed when progestogens are used as contraceptives, see p. 2240.3. For those to be observed when progestogens are used in preparations for menopausal HRT, see p. 2250.1.

Abuse. A case report of abuse of and dependency on progesterone.[1]

1. Keefe DL, Sarrel P. Dependency on progesterone in woman with self-diagnosed premenstrual syndrome. *Lancet* 1996; 347: 1182.

Breast feeding. A large study[1] compared a contraceptive progesterone-releasing vaginal ring and a copper IUD for 1 year in breast-feeding women. There was little difference in infant weight gain during the study, although at 12 months the infants of mothers using the IUD were breast-fed less frequently, receiving more supplementary feeding, and were heavier. There was no adverse effect of progesterone on lactation or infant growth. Further smaller studies[2,3] have also found no adverse effect on lactation or infant growth. The American Academy of Pediatrics has found no reports of adverse effects in breast-fed infants of mothers given progesterone, and therefore considers it to be usually compatible with breast feeding.[4]

1. Sivin I, *et al.* Contraceptives for lactating women: a comparative trial of a progesterone-releasing vaginal ring and the copper T 380A IUD. *Contraception* 1997; 55: 225–32.
2. Díaz S, *et al.* Fertility regulation in nursing women: IX contraceptive performance, duration of lactation, infant growth, and bleeding patterns during use of progesterone vaginal rings, progestin-only pills, Norplant implants, and copper T 380-A intrauterine devices. *Contraception* 1997; 56: 223–32.
3. Massai R, *et al.* Preregistration study on the safety and contraceptive efficacy of a progesterone-releasing vaginal ring in Chilean nursing women. *Contraception* 1999; 60: 9–14.
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 27/06/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies progesterone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1] NAPOS also provides classification for some progestogens—see individual drug monographs, as well as Porphyria under Hormonal Contraceptives (p. 2242.1) and Hormone Replacement Therapy (p. 2250.3).

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. In Hungary, where 30% of all pregnant women were given hormonal support therapy with progestogens during the early 1980s, a case-control study suggested that there was a causal relationship between such treatment and hypospadias in their offspring.[1] Mixed results have been reported in other studies of the association between maternal progestogen use and the risk of hypospadias, but the indications and types of progestogens used in early pregnancy have also changed over time (for example, withdrawal bleeding induced by progestogens as a form of pregnancy testing is no longer used, and progestogen luteal support in early pregnancy is no longer recommended for routine use; see also Miscarriage, p. 2301.2). Nevertheless, results from a more recent case-control study[2] of deliveries between October 1997 and December 2000 suggested an increase in risk of at least twofold.

There have also been reports of nongenital malformations, including limb reduction defects, neural tube defects, and congenital heart malformations, after intra-uterine exposure to progestogens in early pregnancy. However, many analyses of accumulated data have found no evidence of a recognisable malformation syndrome.[3]

For details of individual case reports, see Pregnancy under Dydrogesterone (p. 2270.2), Hydroxyprogesterone (p. 2285.2), Norethisterone (p. 2295.1), and Noretynodrel (p. 2295.3). For the effects of hormonal contraceptive use during early pregnancy, see p. 2242.1. For the risk of ectopic pregnancy with progestogen-only contraceptives, see p. 2236.3.

1. Czeizel A. Increasing trends in congenital malformations of male external genitalia. *Lancet* 1985; i: 462–3.
2. Carmichael SL, *et al.* Maternal progestin intake and risk of hypospadias. *Arch Pediatr Adolesc Med* 2005; 159: 957–62.
3. Brent RL. Nongenital malformations following exposure to progestational drugs: the last chapter of an erroneous allegation. *Birth Defects Res A Clin Mol Teratol* 2005; 73: 906–18.

Veterinary use. An FAO/WHO expert committee examining the risks from residue of veterinary drugs in foodstuffs established an acceptable daily intake for progesterone, but concluded that there would be no need to specify a numerical maximum residue limit for progesterone in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that in the EU the use of steroidal hormones such as progestogens in veterinary practice is restricted, and their use as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 27/06/08)

Interactions

Enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin, and rifampicin may enhance the clearance of progesterone and the progestogens. These interactions are likely to reduce the efficacy of progestogen-only contraceptives (see p. 2242.3), and additional or alternative contraceptive measures are recommended.

Aminoglutethimide markedly reduces the plasma concentrations of medroxyprogesterone acetate and megestrol, possibly through a hepatic enzyme-inducing effect; an increase in progestogen dose is likely to be required.

Since progesterone and other progestogens can influence diabetic control an adjustment in antidiabetic dosage could be required. Progestogens may inhibit ciclosporin metabolism leading to increased plasma-ciclosporin concentrations and a risk of toxicity (see p. 1955.1).

Pharmacokinetics

Progesterone has a short elimination half-life and undergoes extensive first-pass hepatic metabolism when given orally; oral bioavailability is very low although it may be increased somewhat by an oily vehicle and by micronisation. Progesterone is absorbed when given buccally, rectally, or vaginally, and rapidly absorbed from the site of an oily intramuscular injection.

Various derivatives have been produced to extend the duration of action and to improve oral activity. Esters of progesterone derivatives such as hydroxyprogesterone caproate are used intramuscularly, and megestrol acetate is orally active. The ester medroxyprogesterone acetate is used orally and parenterally. 19-Nortestosterone progestogens have good oral activity because the 17-ethinyl substituent slows hepatic metabolism.

Progesterone and the progestogens are highly protein bound; progesterone is bound to albumin and corticosteroid binding globulin; esters such as medroxyprogesterone acetate are mainly bound to albumin; and 19-nortestosterone analogues are bound to sex-steroid binding globulin and albumin. Progesterone is metabolised in the liver to various metabolites including pregnanediol, which are excreted in the urine as sulfate and glucuronide conjugates. Similarly, progestogens undergo hepatic metabolism to various conjugates, which are excreted in the urine. Progesterone is distributed into breast milk.

Reviews.

1. Kuhl H. Comparative pharmacology of newer progestogens. *Drugs* 1996; 51: 188–215.
2. Stanczyk FZ. Structure-function relationships, metabolism, pharmacokinetics and potency of progestins. *Drugs Today* 1996; 32 (suppl B): 1–14.
3. Schindler AE, *et al.* Classification and pharmacology of progestins. *Maturitas* 2003; 46 (suppl 1): S7–S16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Crinone; Gester; Mafel; Progest; Proluton; Utrogestan; *Austral.*: Crinone; Proluton†; *Austria*: Utrogestan; *Belg.*: Crinone; Progestogel; Utrogestan; *Braz.*: Crinone; Evocanil; Utrogestan; *Canad.*: Crinone; Endometrin; Prometrium; *Chile*: Crinone; Fertiring; Hormoral; Progendo; Progering; *China*: Crinone (雪诺同); Lai Ting (来婷); Qi Ning (琪宁); Utrogestan (安琪坦); Yi Ma Xin (益玛欣); *Cz.*: Agolutin; Crinone; Lutinus; Utrogestan; *Denm.*: Crinone; Lutinus; *Fin.*: Crinone; Lugesteron; Lutinus; *Fr.*: Estima; Evapause†; Progestan; Progestogel; Utrogestan; *Ger.*: Crinone; Progestogel; Utrogest; *Gr.*: Crinone; Gestone; Lutorm; Promenorea; TithoGel; Utrogestan; Vasclor; *Hong Kong*: Crinone; Cyclogest; Endometrin; Progestogel; Utrogestan; *Hung.*: Crinone; Utrogestan; *India*: Algest; Alpreg; Arigest; Belgest; Cap Voranin; Corest; Corion NP; Crinone; Cygest; Deltron; Dubagest; Durogest; E-Gest; Endogest; ETS; Evagest; Femicare; Femigest; Firm Up; Forgest; Fulgest; Pydogest; Ges-One; Gesry; Gester-NP; Gesmate; Gestofit; Gestone; Gestorin; Hema; Horpeg; LGP; LPD; Lupigestrone; Lutacare; Manogest; Medpro; Menoxy-N; Micpro; Microgest; Micronat; Miprogen; N-Sanigest; Namgem; Natpreg; Natron; Naturogest; Neogest; Nidagen; NT-Natal MP; Ogest; Onastrone; Remens; Uterone; Voranin; *Indon.*: Crinone; Cygest; *Irl.*: Crinone; Utrogestan; *Israel*: Crinone; Endometrin; Gestone; Utrogestan; *Ital.*: Crinone; Esolut; Lutogin; Progeffik; Prometrium; Prontogest; *Malaysia*: Crinone; Cyclogest; Utrogestan; *Mex.*: Crinone†; Cuerpo Amarillo Puerte; Geprom†; Geslutin; Gestageno; Premastan; Prosphere; Utrogestan; *Mon.*: Menaelle; *Neth.*: Lutinus; Utrogestan; *Norw.*: Crinone; Lutinus; *NZ*: Crinone; Gestone; Utrogestan; *Philipp.*: Crinone; *Pol.*: Luteina; *Port.*: Crinone; Progestogel; Utrogestan; *Rus.*: Crinone (Крайнон); Progestogel (Прожестожель); Utrogestan (Утрожестан); *S.Afr.*: Crinone; Cyclogest; Utrogestan; *Singapore*: Crinone; Cyclogest; Utrogestan; *Spain*: Crinone; Darstin; Progeffik; Progestosol†; Utrogestan; *Swed.*: Crinone; Lutinus; *Switz.*: Crinone; Progestogel; Utrogestan; *Thai.*: Crinone; Cyclogest; Progestogel†; Utrogestan; *Turk.*: Crinone; Cyclogest; Progestan; Progynex; *UK*: Crinone; Cyclogest; Gestone; Utrogestan; *Ukr.*: Endometrin (Эндометрин); Luteina (Лютеина); Progestogel (Прожестожель); Utrogestan (Утрожестан); *USA*: Crinone; Endometrin; Prochieve†; Prometrium; *Venez.*: Crinone; Progendo; Progestogel; Utrogestan.

Multi-ingredient Preparations. *Arg.*: Cristerona; Fempack; Hosterona; Lubriderm; Menstrogen†; Tropivag Plus; *Belg.*: Duogestan; *Fr.*: Florgynal; Trophigil; *Ital.*: Menovis; *Malaysia*: Duogynon; *Mex.*: Damax; Genofort; Lutoginestryl F; Metrigen Puerte; Primoson-F; Proger-F; *Mon.*: Synergon; *Thai.*: Duoton; Phenokinon-F; *Turk.*: Di-Pro; Synergon; *Venez.*: Ginecosid.

Pharmacopoeial Preparations

BP 2014: Progesterone Injection;
USP 36: Progesterone Injectable Suspension; Progesterone Injection; Progesterone Intrauterine Contraceptive System; Progesterone Vaginal Suppositories.

Proligestone *(BAN, rINN)*

Proligeston; Proligestona; Proligestoni; Proligestonum; Пролигестон.

14a,17a-Propylidene dioxypregn-4-ene-3,20-dione.

$C_{24}H_{34}O_4$=386.5

CAS — 23873-85-0.

ATC Vet — QG03DA90.

UNII — 55772LJ01V.

Profile

Proligestone is a progestogen used in veterinary medicine.

Promegestone *(rINN)*

Promegestona; Promégestone; Promegestonum; R-5020; Промегестон.

17a-Methyl-17-propionylestra-4,9-dien-3-one.

$C_{23}H_{30}O_2$=326.5

CAS — 34184-77-5.

ATC — G03DB07.

ATC Vet — QG03DB07.

UNII — 9XE0V2SQYX.

Profile

Promegestone is a progestogen structurally related to progesterone (p. 2300.2). It has been given orally on a cyclical basis, in doses of 125 to 500 micrograms daily, in the treatment of menstrual disorders and mastalgia, and as the progestogen component of menopausal HRT.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Surgestone; *Port.*: Surgestone.

Promestriene *(rINN)*

Promestrien; Promestriène; Promestrieno; Promestrienum; Проместриен.

17β-Methoxy-3-propoxyestra-1,3,5(10)-triene.

$C_{22}H_{32}O_2$=328.5

CAS — 39219-28-8.

ATC — G03CA09.

ATC Vet — QG03CA09.

UNII — GXM4PER6WZ.

Profile

Promestriene is a derivative of estradiol (p. 2271.1) that has been used topically in menopausal atrophic vaginitis, and in seborrhoea and acne.

References.
1. Santos I, Clissold S. Urogenital disorders associated with oestrogen deficiency: the role of promestriene as topical oestrogen therapy. *Gynecol Endocrinol* 2010; 26: 644–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Colpotrophine; *Braz.*: Colpotrofine; *China*: Colpotrophine (更宝芬); *Hong Kong*: Colpotrophine; *Ital.*: Colpotrophine; *Mex.*: Colpotrophine; *Mon.*: Colpotrophine; *Port.*: Colpotrophine; *Singapore*: Colpotrophine†; *Spain*: Colpotrofin; Delipoderm†; *Switz.*: Colpotrophine; *Turk.*: Colpotrophine; *Ukr.*: Colpotrophine (Колпотрофин).

Multi-ingredient Preparations. *China*: Colposeptine (可宝净); *Hong Kong*: Colposeptine; *Mon.*: Colposeptine; *Port.*: Trophoseptine; *Turk.*: Colposeptine; *Ukr.*: Colposeptine (Колпосептин).

Quinestradol *(BAN, rINN)*

Oestriol 3-cyclopentyl Ether; Quinestradiol; Quinestradolum; Хинэстранол

3-Cyclopentyloxyestra-1,3,5(10)-triene-16α,17β-diol

$C_{23}H_{32}O_3$=356.5

CAS — 1169-79-5

UNII — 422L8173W8

Profile

Quinestradol is a synthetic oestrogen that has been given orally for the treatment of menopausal vaginal symptoms.

Quinestrol *(BAN, USAN, rINN)*

17α-Ethinylestradiol 3-cyclopentyl Ether; Quinestrolum; W-3566; Хинэстрол

3-Cyclopentyloxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17β-ol

$C_{25}H_{32}O_2$=364.5

CAS — 152-43-2

UNII — JR0N7XD5GZ

Pharmacopoeias. In *Chin.*

Profile

Quinestrol is a synthetic oestrogen that has a prolonged duration of action and is metabolised to ethinylestradiol (p. 2275.3). Quinestrol has been given orally for the treatment of menopausal symptoms and other conditions arising from oestrogen deficiency. It has also been used as the oestrogen component of combined oral contraceptive preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Qui-Lea.

Multi-ingredient Preparations. *Arg.*: Soluna; *China*: Compound Norgestrel (复方炔诺孕酮); Yueketing (悦可婷).

Raloxifene Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de keoxifeno; Hidrocloruro de raloxifeno; Keoxifene Hydrochloride; LY-139481 (raloxifene); LY-156758; Raloksifen Hidroklorür; Raloxifène, Chlorhydrate de; Raloxifenhydrochlorid; Raloxifeni Hydrochloridum; Raloxifeno, hidrocloruro de; Ралоксифена Гидрохлорид

6-Hydroxy-2-(*p*-hydroxyphenyl)benzo[*b*]thien-3-yl-[2-(1-piperidinoethoxy)phenyl] ketone hydrochloride

$C_{28}H_{27}NO_4S,HCl$=510.0

CAS — 84449-90-1 (raloxifene); 82640-04-8 (raloxifene hydrochloride).

ATC — G03XC01.

ATC Vet — QG03XC01.

UNII — 4F86W47BR6

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

Ph. Eur. 8: (Raloxifene Hydrochloride). An almost white or pale-yellow powder. Very slightly soluble or practically insoluble in water and in acetone; slightly soluble in alcohol.

USP 36: (Raloxifene Hydrochloride). An almost white to pale yellow powder. Very slightly soluble in water, in isopropyl alcohol, and in octanol; slightly soluble in alcohol; sparingly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide; practically insoluble in ether and in ethyl acetate.

Uses and Administration

Raloxifene hydrochloride is a selective oestrogen receptor modulator; it is a benzothiophene that appears to have oestrogen agonist effects on bone and antagonist effects in uterine and breast tissue. It is used, in oral doses of 60 mg daily, for the prevention and treatment of postmenopausal osteoporosis (below). The same dose is also used to reduce the risk of invasive breast cancer in postmenopausal women who have osteoporosis or are at high risk of invasive breast cancer (below).

Reviews.
1. Khovidhunkit W, Shoback DM. Clinical effects of raloxifene hydrochloride in women. *Ann Intern Med* 1999; 130: 431–9.
2. Snyder KR, *et al.* Raloxifene hydrochloride. *Ann J Health-Syst Pharm* 2000; 57: 1669–75.
3. Barrett-Connor E. Raloxifene: risks and benefits. *Ann N Y Acad Sci* 2001; 949: 295–303.
4. Heringa M. Review on raloxifene: profile of a selective estrogen receptor modulator. *Int J Clin Pharmacol Ther* 2003; 41: 331–45.
5. Trémollières F, Ribot C. Indications du raloxifène chez la femme ménopausée. *Gynecol Obstet Fertil* 2006; 34: 147–53.

Administration in renal impairment. Although unexpected, renal impairment reduced raloxifene clearance in a pharmacokinetic study (see p. 2304.1). Licensed product information in the UK contra-indicates the use of raloxifene in severe renal impairment, and in the USA it advises caution in moderate and severe impairment. Nevertheless, raloxifene has been studied in postmenopausal women with renal impairment and severe osteopenia or osteoporosis. An oral dose of 60 mg daily for 1 year was given to 25 women on haemodialysis and found to improve bone mineral density of the lumbar spine, compared with 25 women given placebo; there were no reported adverse effects.[1]

1. Hernández E, *et al.* Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. *Kidney Int* 2003; 63: 2269–74.

Hyperparathyroidism. The effects of raloxifene have been reported in postmenopausal women with mild primary hyperparathyroidism (p. 1170.3). Reductions in markers of bone turnover and plasma concentrations of calcium have been described in an observational report[1] and a small, short-term, placebo-controlled study.[2] An increase in bone mineral density was also detected after 12 months of treatment with raloxifene.[1]

1. Zanchetta JR, Bogado CE. Raloxifene reverses bone loss in postmenopausal women with mild asymptomatic primary hyperparathyroidism. *J Bone Miner Res* 2001; 16: 189–90.
2. Rubin MR, *et al.* Raloxifene lowers serum calcium and markers of bone turnover in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; 88: 1174–8.

Malignant neoplasms of the breast. Studies have found raloxifene to be effective for the prophylaxis of breast cancer (p. 703.2).[1] In a placebo-controlled study[2] of postmenopausal women with osteoporosis and no history of breast cancer (MORE), the use of raloxifene for about 3 years reduced the risk of developing breast cancer. This was seen as a reduction in the risk of invasive oestrogen-receptor positive breast cancer, as there was no effect on the risk of oestrogen-receptor negative disease. The reduction in risk was maintained in an extension[3] of this study (CORE) to a total of 8 years of treatment. Similar results were reported in a large placebo-controlled study (RUTH)[4] of postmenopausal women who were treated for about 5 years. Both MORE/CORE[3] and RUTH[4] reported risk reduction in women at either high or low risk, but the MORE study[3] found the effect to be greater in women with a family history of breast cancer.

In a study[4] of postmenopausal women with a predicted increased risk of breast cancer (STAR), prophylactic raloxifene for up to 5 years was found to be as effective as tamoxifen in reducing the risk of invasive breast cancer.

1. Moen MD, Keating GM. Raloxifene: a review of its use in the prevention of invasive breast cancer. *Drugs* 2008; 68: 2059–83.
2. Cummings SR, *et al.* The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999; 281: 2189–97. Correction. *ibid.*; 282: 2124.
3. Martino S, *et al.* Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst* 2004; 96: 1751–61.
4. Barrett-Connor E, *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; 355: 125–37.
5. Lippman ME, *et al.* Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk. *Clin Cancer Res* 2006; 12: 5242–7.
6. Vogel VG, *et al.* Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006; 295: 2727–41. Corrections. *ibid.*; 296: 2926 and *ibid.* 2007; 298: 973.

Osteoporosis. Raloxifene partially mimics the effects of oestrogens in bone to increase bone mineral density in postmenopausal women.[1,2] The MORE study in 7705 postmenopausal women with osteoporosis (p. 1168.1) found that up to 4 years of raloxifene treatment reduced the risk of vertebral fracture,[3-6] but the risk of nonvertebral fracture did not differ significantly from that in women given placebo.[3,5] A meta-analysis[7] of data from this and other smaller studies concluded that raloxifene reduced the risk of vertebral fracture by between 40 and 49% in postmenopausal women with osteoporosis. NICE recommends raloxifene as an alternative treatment option for the secondary[8] prevention of osteoporotic fragility fractures in high-risk postmenopausal women who are unable to take bisphosphonates. It is not recommended for primary prevention in postmenopausal women.[9]

Small studies suggest that raloxifene may be effective as 'add-back' therapy to prevent the loss of bone mineral density associated with gonadorelin analogue therapy in women[10,11] and men.[12]

1. Clemett D, Spencer CM. Raloxifene: a review of its use in postmenopausal osteoporosis. *Drugs* 2000; 60: 379–411.
2. Cranney A, Adachi JD. Benefit-risk assessment of raloxifene in postmenopausal osteoporosis. *Drug Safety* 2005; 28: 721–30.
3. Ettinger B, *et al.* Multiple Outcomes of Raloxifene Evaluation Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999; 282: 637–45.
4. Maricic M, *et al.* Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. *Arch Intern Med* 2002; 162: 1140–3.
5. Delmas PD, *et al.* Multiple Outcomes of Raloxifene Evaluation Investigators. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002; 87: 3609–17.
6. Qu Y, *et al.* The effect of raloxifene therapy on the risk of new clinical vertebral fractures at three and six months: a secondary analysis of the MORE trial. *Curr Med Res Opin* 2005; 21: 1955–9.
7. Seeman E, *et al.* Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. *Osteoporos Int* 2006; 17: 313–16.
8. NICE. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended): Technology Appraisal 161 (issued October 2008, amended January 2010). Available at: http://www.nice.org.uk/nicemedia/live/11748/47177/47177.pdf (accessed 19/07/10)
9. NICE. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 160 (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA160guidance.pdf (accessed 12/01/09)
10. Palomba S, *et al.* Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. *J Clin Endocrinol Metab* 2002; 87: 4476–81.
11. Palomba S, *et al.* Long-term effectiveness and safety of GnRH agonist plus raloxifene administration in women with uterine leiomyomas. *Hum Reprod* 2004; 19: 1308–14.
12. Smith MR, *et al.* Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2004; 89: 3841–6.

Adverse Effects

The most common adverse effects of selective oestrogen receptor modulators such as raloxifene are hot flushes, leg cramps, and a flu-like syndrome. Raloxifene is associated with an increased risk of venous thromboembolic events including deep-vein thrombosis, pulmonary embolism, and retinal vein thrombosis, particularly during the first 4 months of treatment. Peripheral oedema has also been reported. Rashes, gastrointestinal disturbances, thrombocytopenia, increased blood pressure, headache including migraine, and mild breast symptoms such as pain, enlargement, and tenderness have occurred very rarely.

Incidence of adverse effects. An observational cohort study[1] examined postmarketing adverse events that occurred during raloxifene use in primary care in England. The cohort of 13 987 patients consisted largely of women aged about 62 years, who were receiving raloxifene for the prevention or treatment of osteoporosis. Of the 461 events reported, the most common included flushing, headache or migraine, malaise or lassitude, cramp, oedema, sweating, depression, weight gain, and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, and diarrhoea. Other less common effects included mastalgia and other breast symptoms, vaginal bleeding, thrombophlebitis, and visual disturbances. Rare events included cerebrovascular attack, transient ischaemic attack, pulmonary embolus, deep-vein thrombosis, bullous eruption, leucopenia, thrombocytopenia, upper gastrointestinal haemorrhage, and perforated duodenal ulcer.

See also Effects on the Cardiovascular System, below.

1. Layton D, *et al.* Safety profile of raloxifene as used in general practice in England: results of a prescription-event monitoring study. *Osteoporosis Int* 2005; 16: 490–500.

Effects on the cardiovascular system. The incidence of cardiovascular effects associated with raloxifene treatment was examined in the 4-year Multiple Outcomes of Raloxifene Evaluation (MORE), which studied its effects in postmenopausal women with osteoporosis, and in a subsequent 4-year follow-up (Continuing Outcomes Relevant to Evista: CORE).[1] There were 7705 women in the MORE study, of whom 4011 were enrolled in CORE. Overall no significant differences were seen between active treatment and placebo for any cardiovascular event over the 8 years; the calculated incidence was 72 per 10 000 woman-years in those taking raloxifene and 62 per 10 000 in the placebo

group. Another large placebo-controlled study[2] (Raloxifene Use for The Heart: RUTH) investigated the cardiovascular effects of raloxifene in postmenopausal women with, or at increased risk of, ischaemic heart disease. After treatment for about 5 years there was no significant difference between the groups for overall cardiovascular events and related deaths. However, in those given raloxifene there was an increased risk of fatal stroke (absolute risk increase, 0.7 per 1000 women-years) and venous thromboembolism (1.2 per 1000 women-years).

1. Ensrud K, *et al.* Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. *Am J Cardiol* 2006; 97: 520–7.
2. Barrett-Connor E, *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; 355: 125–37.

Effects on the liver. Hepatitis, probably associated with the drug, occurred in a woman a month after starting raloxifene.[1] Non-alcoholic steatohepatitis was associated with raloxifene in a woman with minor liver dysfunction, a fatty liver, and a family history of cryptogenic liver cirrhosis.[2] Her liver function worsened during the 3 months after starting the drug, and had returned to baseline 3 months after stopping.

1. Vilches AR, *et al.* Raloxifene-associated hepatitis. *Lancet* 1998; 352: 1524–5.
2. Takamura T, *et al.* Selective estrogen receptor modulator raloxifene-associated aggravation of nonalcoholic steatohepatitis. *Intern Med* 2007; 46: 579–81.

Precautions

Raloxifene should be avoided in women with active venous thromboembolism, or a history of thromboembolic disorders. It should be stopped at least 72 hours before periods of prolonged immobilisation, such as post-surgical recovery. Raloxifene should be used with caution in women with risk factors for venous thromboembolism including congestive heart failure or active malignancy, or risk factors for stroke such as transient ischaemic attack or atrial fibrillation. It should be avoided in hepatic and severe renal impairment, and used with caution in moderate renal impairment (but see also Administration in Renal Impairment, p. 2303.2).

Raloxifene had adverse effects in *animal* teratogenicity studies and should not be used in women who are or may become pregnant. It should not be given to women with undiagnosed uterine bleeding. An increase in triglycerides has been reported in some women with a history of hypertriglyceridaemia caused by oestrogen therapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies raloxifene 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 06/10/11)

Interactions

Colestyramine reduces the absorption and enterohepatic recycling of raloxifene, and they should not be given together. Raloxifene may decrease the efficacy of warfarin. Levothyroxine requirements may also be increased with raloxifene use (see Sex Hormones under the interactions of Levothyroxine Sodium, p. 2342.2).

Fibrates. Cholestasis developed when *fenofibrate* was given to a woman who had been on raloxifene therapy for about 3 years.[1] The authors reviewed other rare reports of liver reactions to either raloxifene or fibrates and suggested that the reaction was likely to be due to an interaction, although the mechanism was not clear.

1. Lucena MI, *et al.* Prolonged cholestasis after raloxifene and fenofibrate interaction: a case report. *World J Gastroenterol* 2006; 12: 5244–6.

Pharmacokinetics

Raloxifene is absorbed from the gastrointestinal tract and undergoes extensive first-pass hepatic metabolism to the glucuronide conjugates. It is highly bound to plasma proteins, mainly albumin and α_1-acid glycoprotein. Raloxifene undergoes enterohepatic recycling, and has a half-life of about 27 hours. It is excreted almost entirely in the faeces.

Renal impairment. The pharmacokinetics of raloxifene are not expected to be affected by renal impairment because the renally excreted fraction is only about 6% in healthy subjects. However, a study[1] in male subjects found the clearance of a single 120-mg oral dose to be significantly reduced in 10 men with renal impairment (creatinine clearance 24 to 51 mL/minute) compared with a group of 10 with normal renal function. It was calculated that steady-state concentrations could be about 2.3 times higher in patients with renal impairment. The authors suggested that this unexpected result might be due to reduced metabolic clearance in the renal tubules or by impairment of biliary excretion of raloxifene glucuronides by uraemic toxins.

1. Crock D, *et al.* Raloxifene pharmacokinetics in males with normal and impaired renal function. *Br J Clin Pharmacol* 2005; 59: 479–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Evista; Ketidin; Oseofem†; *Raxeto*; *Austral.*: Evista; *Austria*: Evista; *Belg.*: Evista; *Braz.*: Evista; *Canad.*: Evista; *Chile*: Evista; *China*: Bei Bang (贝邦); Evista (易维特); *Cz.*: Evista; Optruma; Ralfeen; *Denm.*: Evista; *Fin.*: Evista; *Fr.*: Evista; Optruma; *Ger.*: Evista; Optruma; *Gr.*: Evista; *Hong Kong*: Evista; *Hung.*: Evista; *India*: Bonmax; Bontact; Esserm; Estroact; Evomate; Fiona; Gynista; Osral; Ralista; *Indon.*: Evista; *Irl.*: Evista; Optruma; Raloxiep; *Israel*: Evista; *Ital.*: Evista; Optruma; *Jpn*: Evista; *Malaysia*: Evista; *Mex.*: Evista; *Neth.*: Evista; Optruma; RaloMeer; Ralover; Raloxa; Raloxiep; RaloxStar; Raloxten; *Norw.*: Evista; *NZ*: Evista; *Philipp.*: Evista; *Pol.*: Evista; Optruma; *Port.*: Evista; Optruma; *Rus.*: Evista (Эвиста); *S.Afr.*: Evista; *Singapore*: Evista; *Spain*: Evista; Optruma; *Swed.*: Evista; *Switz.*: Evista; *Thai.*: Celvista; *Turk.*: Evista; *UK*: Evista; *USA*: Evista; *Venez.*: Evista.

Pharmacopoeial Preparations
USP 36: Raloxifene Hydrochloride Tablets.

Stanozolol *(BAN, USAN, rINN)* ⊗

Androstanazol; Androstanazole; Estanazol; Estanozolol; Methylstanazole; Metistanazol; NSC-43193; Stanotsololi; Stanozololis; Stanozololum; Stanozolum; Sztanozolol; Win-14833; Станозолол.

17α-Methyl-2′*H*-5α-androst-2-eno[3,2-*c*]pyrazol-17β-ol.

$C_{21}H_{32}N_2O$=328.5

CAS — 10418-03-8.

ATC — A14AA02.

ATC Vet — QA14AA02.

UNII — 4R1V89P8V3.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of stanozolol:

Iron Brew.

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

Ph. Eur. 8: (Stanozolol). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; soluble in dimethylformamide; very slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Stanozolol). An odourless crystalline powder occurring in 2 forms; needles melt at about 155 degrees and prisms at about 235 degrees. Insoluble in water; soluble 1 in 41 of alcohol, 1 in 74 of chloroform, and 1 in 370 of ether; slightly soluble in acetone and in ethyl acetate; soluble in dimethylformamide; very slightly soluble in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Stanozolol has anabolic and androgenic properties (see Testosterone, p. 2305.2). As with other anabolic steroids, stanozolol has been used for breast cancer in postmenopausal women, and for anaemias, osteoporosis, and catabolic disorders. It has been given in oral doses of 2 mg every 8 to 12 hours, or 50 mg by intramuscular injection every 2 or 3 weeks.

Stanozolol may be used in the management of hereditary angioedema (see below).

Hereditary angioedema. Stanozolol raises serum concentrations of C1 esterase inhibitor and has been used to prevent attacks of hereditary angioedema (p. 2485.2). Initial doses are titrated down to the lowest effective prophylactic dose, to minimise adverse effects from long-term use. Stanozolol is typically given orally in doses of 1 to 2 mg daily or on alternate days,[1,2] and possibly less frequently,[3] although doses of up to 5 mg once or twice daily may be necessary.[4] Additional short-term prophylaxis may be used in situations expected to provoke an attack, such as surgery or dental procedures. Stanozolol 2 mg three times daily may be used for this, but should be started about 5 to 7 days before the procedure,[1] and continued for 48 hours after.[4] A higher dose of 4 mg every 6 hours, for 5 days before the procedure, has also been reported.[3]

Attenuated androgens are not usually given in the acute management of hereditary angioedema. However, the early use of up to 16 mg daily of stanozolol may shorten the duration of an attack of peripheral swelling.[4] A dose of stanozolol 4 mg every 6 to 8 hours, with fresh frozen plasma, has also been used in the early management of severe acute attacks.[3]

1. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; 114: 10–16.
2. Banerji A, *et al.* Hereditary angioedema: a current state-of-the-art review, V: attenuated androgens for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 2008; 100 (suppl 2): S19–S22.
3. Sloane DE, *et al.* Hereditary angioedema: safety of long-term stanozolol therapy. *J Allergy Clin Immunol* 2007; 120: 654–8.
4. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; 139: 379–94. Correction. *Ibid.*; 141: 189–90. [dose]

Vascular disorders. Stanozolol has been used in the treatment of vascular manifestations of Behçet's syndrome. It has also been reported to promote fibrinolysis in vascular disorders, and has been tried in various conditions. However, most studies have been noncomparative and in small numbers of patients, and results have been variable.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3). As with other 17α-alkylated compounds stanozolol may produce hepatotoxicity, and liver function should be monitored. It is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Haematocrit and haemoglobin concentrations should also be monitored.

Because of its androgenic effects it has been recommended that stanozolol should not be used to treat hereditary angioedema in premenopausal women except in life-threatening situations.

Effects on the kidneys. Renal failure with cholestatic jaundice has been reported with stanozolol (see below).

Effects on the liver. Cholestatic jaundice has been reported with stanozolol,[1-3] in some cases with acute tubular necrosis and renal failure.[4]

1. Slater SD, *et al.* Jaundice induced by stanozolol hypersensitivity. *Postgrad Med J* 1976; 52: 229–32.
2. Evely RS, *et al.* Severe cholestasis associated with stanozolol. *BMJ* 1987; 294: 612–13.
3. Martínez B, *et al.* Colestasis inducida por consumo de estanozolol. *Rev Esp Enferm Dig* 2006; 98: 219–20.
4. Yoshida EM, *et al.* At what price, glory? Severe cholestasis and acute renal failure in an athlete abusing stanozolol. *Can Med Assoc J* 1994; 151: 791–3.

Effects on the nervous system. Benign intracranial hypertension developed in an elderly woman receiving stanozolol; CSF pressure returned to normal after stanozolol was stopped.[1]

1. Tully MP, *et al.* Intracranial hypertension associated with stanozolol. *DICP Ann Pharmacother* 1990; 24: 1234.

Interactions

As mentioned under Testosterone, p. 2308.3, anabolic steroids may enhance the activity of various drugs. For the effect of stanozolol on some anticoagulants, see p. 1535.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Stromba†; *India*: Menabol; Neurabol; *Spain*: Winstrol; *Thai.*: Stanztab.

Multi-ingredient Preparations. *Thai.*: Cetabon†.

Pharmacopoeial Preparations
USP 36: Stanozolol Tablets.

Testis Extracts ⊗

Extractos testiculares; Testicular Extracts; Тестикулярный Экстракт.

Profile

Testis extracts are usually of bovine origin and have been used in a variety of disorders. They have been given to elderly men as androgenic supplements. They have also been used topically, often in preparations containing other mammalian tissue extracts, in the treatment of peripheral circulatory or musculoskeletal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: FegaCoren; *Hong Kong*: Sessoforte†; Wari-Procomil†.

Homoeopathic Preparations. *Fr.*: Amphosca Orchitine; *Ger.*: NeyChon Nr 68; NeyChondrin Nr 68-Sol†; NeyDil Nr 66†; Neydin-M†; NeyGero Nr 64; NeyGeront Nr 64-Sol L†; NeyGeront Vitalkapsein A; NeyLing Nr 66; NeySol L 66†; *Neth.*: Chavita 1; Emvita 3; *USA*: Estrex.

Testosterone (BAN, rINN) ⊗

Testosteroni, Testosterona, Testosteronas, Testostérone, Testosteronum, Tesztoszteron, Тестостерон

17β-Hydroxyandrost-4-en-3-one

$C_{19}H_{28}O_2$=288.4

CAS — 58-22-0

ATC — G03BA03

ATC Vet — QG03BA03

UNII — 3XMK78S47O

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of testosterone:

T-Stoff.

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

Ph. Eur. 8: (Testosterone). A white or almost white, crystalline powder, or colourless or yellowish-white crystals. Practically insoluble in water and in fatty oils; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Testosterone). White or slightly creamy-white, odourless, crystals or crystalline powder. Practically insoluble in water; soluble 1 in 6 of dehydrated alcohol, 1 in 2 of chloroform, and 1 in 100 of ether; soluble in dioxan and in vegetable oils. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Testosterone Cipionate (BANM, rINNM) ⊗

Cipionato de testosterona; Testosterona, cipionato de; Testosterone Cipionate de; Testosterone Cyclopentylpropionate; Testosterone Cypionate; Testosteroni Cipionas; Тестостерона Ципионат

3-Oxoandrost-4-en-17β-yl 3-cyclopentylpropionate; 17β-Hydroxyandrost-4-en-3-one cyclopentanepropionate; 17β-(3-Cyclopentyl-1-oxopropoxy)androst-4-en-3-one.

$C_{27}H_{40}O_3$=412.6

CAS — 58-20-8

ATC — G03BA03

ATC Vet — QG03BA03

UNII — M0XW1UBI14

Pharmacopoeias. In *US.*

USP 36: (Testosterone Cypionate). A white or creamy-white, crystalline powder, odourless or has a slight odour. Insoluble in water; freely soluble in alcohol, in chloroform, in dioxan, and in ether; soluble in vegetable oils. Protect from light.

Testosterone Decanoate (BANM, rINNM) ⊗

Decanoato de testosterona; Testosteron Dekanoat; Testosterona, decanoato de; Testosterondecanoat; Testostérone, décanoate de; Testosteroni decanoas; Тестостерона Деканоат

3-Oxoandrost-4-en-17β-yl decanoate; 17β-Hydroxyandrost-4-en-3-one decanoate.

$C_{29}H_{44}O_3$=442.7

CAS — 5721-91-5

ATC — G03BA03

ATC Vet — QG03BA03

UNII — UW60LAO6S

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

Ph. Eur. 8: (Testosterone Decanoate). A white or almost white powder. Practically insoluble in water; very soluble in anhydrous alcohol, in acetone, and in dichloromethane; freely soluble in fatty oils. Store at a temperature of 2 degrees to 8 degrees.

Testosterone Enantate (BANM, rINNM) ⊗

Enantato de testosterona; NSC-17591; Testosteron enantat; Testosterona, enantato de; Testostérone, Enantate de; Testosterone Enanthate; Testosterone Heptanoate; Testosterone Heptylate; Testosteronenantat; Testosteroni Enantas; Testosteronienantaatti; Testosterono enantatas; Testosteroni-enantan; Tesztoszteronönantát; Тестостерона Энантат

3-Oxoandrost-4-en-17β-yl heptanoate; 17β-Hydroxyandrost-4-en-3-one heptanoate.

$C_{26}H_{40}O_3$=400.6

CAS — 315-37-7

ATC — G03BA03

ATC Vet — QG03BA03

UNII — 5Z653Z78N9

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

Ph. Eur. 8: (Testosterone Enantate). A white or yellowish-white crystalline powder. Practically insoluble in water; very soluble in dehydrated alcohol; freely soluble in fatty oils. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Testosterone Enanthate). A white or creamy-white crystalline powder. It is odourless or has a faint odour characteristic of heptanoic acid. Insoluble in water; very soluble in ether; soluble in vegetable oils. Store in a cool place.

Testosterone Isocaproate (BANM, rINNM) ⊗

Isocaproato de testosterona; Testosteroni Isokaproat; Testosterona, isocaproato de; Testostérone, isocaproate de; Testosterone Isohexanoate; Testosteroni Isocaproas; Testosteroni-isocaproat; Тестостерона Изокапронат

3-Oxoandrost-4-en-17β-yl 4-methylpentanoate; 17β-Hydroxyandrost-4-en-3-one 4-methylpentanoate.

$C_{25}H_{38}O_3$=386.6

CAS — 15262-86-9

ATC — G03BA03

ATC Vet — QG03BA03

UNII — X85T05GYDM

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

Ph. Eur. 8: (Testosterone Isocaproate). A white or almost white powder. Practically insoluble in water; very soluble in acetone and in dichloromethane; freely soluble in fatty oils.

Testosterone Phenylpropionate (BANM, rINNM) ⊗

Fenilpropionato de testosterona; Testosteron Fenilpropionat; Testosterona, fenilpropionato de; Testostérone, Phénylpropionate de; Testosteroni Phenylpropionas; Тестостерона Фенилпропионат

3-Oxoandrost-4-en-17β-yl 3-phenylpropionate; 17β-Hydroxyandrost-4-en-3-one 3-phenylpropionate.

$C_{28}H_{36}O_3$=420.6

CAS — 1255-49-8

ATC — G03BA03

ATC Vet — QG03BA03

UNII — 8GN84GWX51

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2014: (Testosterone Phenylpropionate). A white to almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

Testosterone Propionate (BANM, rINNM) ⊗

NSC-9166; Propionato de testosterona; Testosteron Propionat; Testosterona, propionato de; Testostérone, Propionate de; Testosteroni Propionas; Testosteronipropionaatti; Testosterono propionatas; Testosteronpropionat; Testosteron-propionát; Testosteronu propionian; Tesztoszteronpropionát; Тестостерона Пропионат

3-Oxoandrost-4-en-17β-yl propionate; 17β-Hydroxyandrost-4-en-3-one propionate.

$C_{22}H_{32}O_3$=344.5

CAS — 57-85-2

ATC — G03BA03

ATC Vet — QG03BA03

UNII — WI93Z9138A

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

Ph. Eur. 8: (Testosterone Propionate). A white or almost white powder or colourless crystals. Practically insoluble in water; freely soluble in alcohol and in acetone; soluble in fatty oils.

USP 36: (Testosterone Propionate). White or creamy-white, odourless, crystals or crystalline powder. Insoluble in water; freely soluble in alcohol, in dioxan, in ether, and in other organic solvents; soluble in vegetable oils. Protect from light.

Testosterone Undecylate (rINNM) ⊗

Org-538; Testosteron Undekanoat; Testosterona, undecilato de; Testosterone Undecanoate (USAN); Testosterone Undecanoate (BANM); Testostérone, Undécylate de; Testosteroni Undecylas; Undecilato de testosterona; Тестостерона Ундекоинат

3-Oxoandrost-4-en-17β-yl undecanoate; 17β-Hydroxyandrost-4-en-3-one undecanoate.

$C_{30}H_{48}O_3$=456.7

CAS — 5949-44-0

ATC — G03BA03

ATC Vet — QG03BA03

UNII — H16A5VCT9C

Pharmacopoeias. In *Chin.*

Uses and Administration

The natural hormone testosterone and its derivatives have anabolic and androgenic properties (for further details, see p. 2231.1).

The primary indication for androgens, such as testosterone or its esters, is as replacement therapy in **male hypogonadal disorders** (p. 2306.3) caused by either pituitary or testicular disorders or in hypogonadism following orchidectomy. Testosterone may be used as a subcutaneous implant in a dose of 100 to 600 mg; plasma concentrations of testosterone are usually maintained within the physiological range for 4 to 5 months with a dose of 600 mg. It may also be given by transdermal delivery systems. Patches are applied to the back, abdomen, thighs or upper arms to supply 2 to 7.5 mg daily. A scrotal patch has been used, but is no longer widely available. Hydroalcoholic gels containing 1 or 2% testosterone are also used; they are applied daily to the shoulders and upper arms, abdomen, or thighs, depending on the preparation. About 10% of the applied dose is absorbed across the skin to provide a systemic dose of testosterone 5 to 10 mg. An alcoholic solution containing 30 mg testosterone per 1.5 mL for application to the axillae is also used. The recommended starting dose is 60 mg applied once daily, as 30 mg to each axilla. The dose may be adjusted within a range of 30 to 120 mg daily. A sustained-release adhesive buccal system that contains testosterone 30 mg is applied twice daily; by this route the systemic dose is about 3 mg. Testosterone has also been given by intramuscular injection in a dose of up to 50 mg two or three times weekly, but testosterone esters are generally preferred by this route.

The testosterone esters are usually formulated as oily solutions for intramuscular use to give a prolonged duration of action. Doses that have been used for the various esters are:

- testosterone cipionate 50 to 400 mg every 2 to 4 weeks
- testosterone enantate 50 to 400 mg every 2 to 4 weeks, or an initial dose of 250 mg every 2 to 3 weeks followed by maintenance dosing every 3 to 6 weeks
- testosterone propionate up to 50 mg two or three times weekly
- testosterone undecylate 1 g every 10 to 14 weeks

The isocaproate, phenylpropionate, and propionate esters may be given as a combined intramuscular preparation, sometimes also containing testosterone decanoate. Testosterone hexahydrobenzoate, testosterone hexahydrobenzylcarbonate, and testosterone isobutyrate have also been used. The undecylate ester is also given orally in an initial dose of 120 to 160 mg daily, in 2 divided doses, for 2 to 3 weeks, followed by a maintenance dose of 40 to 120 mg daily. See p. 2306.1 for some doses of testosterone used in children.

Androgens and anabolic steroids have sometimes been used with oestrogens in the management of menopausal symptoms in **women.** Intramuscular injections containing an androgen and an oestrogen have been used for the treatment of menopausal vasomotor symptoms, and testosterone implants have been given as an adjunct to menopausal HRT for symptoms such as decreased libido. A transdermal patch was also available for the treatment of hypoactive sexual desire disorder in women with surgically induced menopause (bilateral oophorectomy and hysterectomy) who were receiving oestrogen therapy. However, there are concerns about the use of these preparations and conflicting opinion as to their usefulness (see p. 2307.1). The use of androgens and anabolic steroids in women with osteoporosis is no longer advocated because their adverse effects essentially outweigh any benefit they may produce. In postmenopausal women androgens, and sometimes anabolic steroids are occasionally used in the hormonal therapy of disseminated breast carcinoma but care should be taken to choose a compound with a lower masculinising effect; the short-acting synthetic compounds are usually preferred for such purposes. Testosterone enantate has been used in doses of 200 to 400 mg every 2 to 4 weeks by intramuscular injection.

Anabolic steroids, and sometimes androgens, have been used in the treatment of refractory anaemias characterised by deficient red cell production, such as aplastic anaemia (p. 1121.3). Anabolic steroids and synthetic androgens with an attenuated action (sometimes known as 'attenuated androgens') such as danazol are also used in the management of hereditary angioedema (p. 2485.2).

Topical androgens may be used in the treatment of lichen sclerosus (p. 2307.1).

Androgens and anabolic steroids have been used for their anabolic properties in various catabolic states (see Anabolic Effects, p. 2306.1).

Testosterone hemisuccinate is an ingredient of preparations that have been promoted for the management of cataracts.

General reviews of androgens and anabolic steroids.

1. Hickson RC, *et al.* Adverse effects of anabolic steroids. *Med Toxicol Adverse Drug Exp* 1989; 4: 254–71.
2. Bagatell CJ, Bremner WJ. Androgens in men—uses and abuses. *N Engl J Med* 1996; 334: 707–14.
3. Conway AJ, *et al.* Use, misuse and abuse of androgens: the Endocrine Society of Australia consensus guidelines for androgen prescribing. *Med J Aust* 2000; 172: 220–4. Correction. *ibid.*; 334. Also available at: http://www.mja.com.au/public/issues/172_05_060300/conway/conway.html (accessed 13/11/07)
4. Handelsman DJ. Testosterone: use, misuse and abuse. *Med J Aust* 2006; 185: 436–9.

Administration in children. Testosterone is used in adolescent males with hypogonadism, and has been used in constitutionally delayed puberty. It has also been used to reduce final height in boys with constitutional tall stature (see below).

Although not licensed in the UK for the induction and maintenance of **sexual maturation** in boys over 12 years of age, the *BNFC* recommends a dose of testosterone undecylate 40 mg orally on alternate days; this may be increased up to 120 mg daily according to response. Alternatively, testosterone enantate may be given by deep intramuscular injection in doses of 25 to 50 mg/m^2 every month, increasing every 6 to 12 months according to response. Testosterone propionate 50 mg may be given once weekly by intramuscular injection. Although no longer marketed in the UK, an injection containing a combination of testosterone esters (isocaproate 40 mg, phenylpropionate 40 mg, and propionate 20 mg) has been given intramuscularly, once each month for 3 doses, for delayed puberty. The *BNFC* also suggests that an implant may be used in children over 16 years of age for maintenance of sexual maturation. See p. 2305.2 for doses. However, great care is necessary when using androgens for such conditions as bone growth and final height may be inhibited by the early fusion of the epiphyses. Extemporaneously prepared testosterone 5% cream has been applied topically, 3 times daily for 3 weeks, in the management of microphallus (the alcohol in proprietary gels can cause irritation).

Growth hormone provocation testing may be used in the diagnosis of growth hormone deficiency in children with growth retardation (p. 1918.3). However, the response can be blunted in prepubertal and peripubertal children, resulting in false negative results. Hormonal **pituitary priming** using testosterone has been tried in boys in order to increase responsiveness to the test,[1-3] although there appears to be no consensus on such use.[4] One regimen that has been used is a single intramuscular dose of a product containing a combination of testosterone esters (isocaproate 40 mg, phenylpropionate 40 mg, and propionate 20 mg), given 3 to 5 days before the test.

1. Loche S, *et al.* The growth hormone response to hexarelin in children: reproducibility and effect of sex steroids. *J Clin Endocrinol Metab* 1997; **82**: 861–4.
2. Coutant R, *et al.* Body composition, fasting leptin, and sex steroid administration determine GH sensitivity in peripubertal short children. *J Clin Endocrinol Metab* 2001; **86**: 5805–12.
3. Gönç EN, *et al.* Comparison of stimulated growth hormone levels in primed versus unprimed provocative tests: effect of various testosterone doses on growth hormone levels. *Horm Res* 2001; **56**: 32–7.
4. Growth Hormone 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 22/08/08)

Anabolic effects. The androgens generally possess anabolic activity and were formerly used to increase weight in patients suffering from emaciation or debilitating diseases but efficacy was doubtful. The anabolic steroids were developed in order to enhance the ability to build proteins and diminish the virilising and masculinising effects of the natural androgens, but all anabolics retain some androgenic activity. The anabolic steroids have again, like the androgens, been used in an attempt to produce weight gain in cachexia and wasting diseases (p. 2289.3).

The anabolic steroids and androgens have been the subject of much misuse and abuse by athletes, sports persons, and body builders (see under Precautions, p. 2308.2) in an attempt to increase muscle mass and body-weight but such use cannot be justified.

References to the anabolic effects of testosterone.

1. Bhasin S, *et al.* The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996; **335**: 1–7.
2. Basaria S, *et al.* Anabolic-androgenic steroid therapy in the treatment of chronic diseases. *J Clin Endocrinol Metab* 2001; **86**: 5108–17.
3. Kong A, Edmonds P. Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis. *Lancet Infect Dis* 2002; **2**: 692–9.
4. Johns K, *et al.* Anabolic steroids for the treatment of weight loss in HIV-infected individuals. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 13/11/07).

Antineoplastic-induced infertility. For reference to the use of testosterone to preserve gonadal function during cyclophosphamide therapy, see Effects on Reproductive Potential, p. 773.1.

Constitutionally delayed puberty. Testosterone enantate given by intramuscular injection every 1 to 2 months for periods ranging from 3 months to several years, produced beneficial effects in boys with constitutionally delayed puberty and growth;[1,2] growth rate increased, sexual and skeletal maturation were stimulated, and full height potential did not appear to be compromised. However, it has been pointed out that repeated intramuscular injections are painful and are disliked by adolescents;[3] oral testosterone undecylate or oxandrolone have been shown to be effective in the treatment of delayed puberty and growth in boys,[4,5] and may be preferred.[3] It should be noted that giving androgens to boys with constitutional delay of growth and puberty is controversial (see p. 2252.1). For reference to the use of testosterone in boys with delayed puberty due to hypogonadism see below.

1. Donaldson MDC, Savage DCL. Testosterone therapy in boys with delayed puberty. *Arch Dis Child* 1987; **62**: 647–8.
2. Richman RA, Kirsch LR. Testosterone treatment in adolescent boys with constitutional delay in growth and development. *N Engl J Med* 1988; **319**: 1563–7.
3. Kelnar CJH. Treatment of the short, sexually immature adolescent boy. *Arch Dis Child* 1994; **71**: 285–7.
4. Albanese A, *et al.* Oral treatment for constitutional delay of growth and puberty in boys: a randomised trial of an anabolic steroid or testosterone undecanoate. *Arch Dis Child* 1994; **71**: 315–17.
5. Brown DC, *et al.* A double blind, placebo controlled study of the effects of low dose testosterone undecanoate on the growth of small for age, prepubertal boys. *Arch Dis Child* 1995; **73**: 131–5.

Constitutionally tall stature. Supraphysiological doses of androgens have been used to *reduce* final height in tall adolescent boys. Testosterone esters in monthly doses of up to 1 g by intramuscular injection have been used.[1] Preliminary evidence after a mean of 10 years follow-up suggests that there was no long-term effect on reproductive function.[2] For reference to the use of testosterone to *increase* growth rate, see Constitutionally Delayed Puberty, above.

1. Drop SLS, *et al.* Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 1998; **19**: 540–58.
2. de Waal WJ, *et al.* Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. *Arch Dis Child* 1995; **73**: 311–15.

Dementia. There has been some suggestion that age-related reduction in endogenous testosterone may have a role in cognitive decline in men (see Dementia, p. 388.1). In a longitudinal study[1] of 574 men who were followed for about 19 years, a lower calculated concentration of free testosterone was found to be one of several risk factors associated with the development of Alzheimer's disease. A possible role for testosterone treatment has therefore been proposed and some preliminary studies have been undertaken. A small short-term study[2] of older men with Alzheimer's disease or mild cognitive impairment reported improvements in some measures of cognitive function in patients given intramuscular testosterone. In another study,[3] however, testosterone applied as a topical gel was reported to improve quality of life as scored by the caregivers of men with mild Alzheimer's disease, but to have no significant effect on quality of life in healthy elderly men or on cognitive function in either group. The possible role of androgens has been reviewed.[4,5]

1. Moffat SD, *et al.* Free testosterone and risk for Alzheimer disease in older men. *Neurology* 2004; **62**: 188–93.
2. Cherrier MM, *et al.* Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology* 2005; **64**: 2063–8.
3. Lu PH, *et al.* Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. *Arch Neurol* 2006; **63**: 177–85.
4. Fuller SJ, *et al.* Androgens in the etiology of Alzheimer's disease in aging men and possible therapeutic interventions. *J Alzheimers Dis* 2007; **12**: 129–42.
5. Drummond ES, *et al.* Androgens and Alzheimer's disease. *Curr Opin Endocrinol Diabetes Obes* 2009; **16**: 254–9.

Erectile dysfunction. Although testosterone is known to enhance libido its physiological role in erection is still not fully understood. Studies have produced mixed results, but suggest that men with sexual or erectile dysfunction (p. 2348.2) and low baseline concentrations of testosterone may derive some benefit from testosterone monotherapy;[1,2] the use of testosterone may also have some benefit in those who have responded poorly to phosphodiesterase type-5 inhibitors.[1,3] However, because of limited evidence and the potential for adverse effects, therapy should probably be limited to men with severe hypogonadism[1,2] (see also Hypogonadism, below).

For reference to the use of a cream containing testosterone, isosorbide dinitrate, and codergocrine mesilate in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p. 1392.2.

1. Mikhail N. Does testosterone have a role in erectile function? *Am J Med* 2006; **119**: 373–82.
2. Bolona ER, *et al.* Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007; **82**: 20–8.
3. Shabsigh R, *et al.* The evolving role of testosterone in the treatment of erectile dysfunction. *Int J Clin Pract* 2006; **60**: 1087–92.

Gender reassignment. Testosterone is used in female-to-male transsexuals to develop and maintain secondary sexual characteristics.[1,2] A testosterone ester, or a combination of esters, is usually given by intramuscular injection in doses of 200 to 250 mg every 2 weeks, adjusted according to response.[2,3] Alternatively, testosterone undecylate 1 g may be given once every 10 to 12 weeks.[3] Oral or transdermal testosterone is less commonly used, and the addition of a progestogen may be needed to fully suppress menstruation in non-oophorectomised patients.[2]

1. Moore E, *et al.* Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *J Clin Endocrinol Metab* 2003; **88**: 3467–73.
2. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
3. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93**: 19–25.

Heart failure. Low serum-testosterone concentrations have been reported in men with chronic heart failure (p. 1262.3). A study in men with moderate heart failure and low or low-normal testosterone concentrations found that 12 months of transdermal testosterone therapy improved symptoms of heart failure and exercise capacity.[1] The mechanism of benefit was unclear. A subsequent study reported similar benefits,[2] which were considered to be due to metabolic and peripheral effects.

1. Malkin CJ, *et al.* Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J* 2006; **27**: 57–64.
2. Caminiti G, *et al.* Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol* 2009; **54**: 919–27.

Hypogonadism. Replacement therapy with testosterone or a testosterone ester is the standard treatment for *primary hypogonadism* in men (see p. 2252.3). The androgen is often given as an intramuscular depot injection of one of the esters, although subcutaneous implants, oral formulations, transdermal systems, topical gels and solutions and a buccal preparation are also used (for doses see Uses and Administration, p. 2305.2).[1-3] Testosterone is also used to promote masculinisation in hypogonadal adolescent boys,[4,5] and is of value in the prevention of osteoporosis in hypogonadal men.[6,7] Testosterone has a negative feedback effect on gonadotrophin secretion, therefore any remaining spermatogenesis is generally suppressed; androgens are thus rarely useful in reversing male infertility (p. 2253.1). Recommendations for monitoring therapy have been made.[3,8]

Transdermal testosterone may possibly be of benefit as an adjunct to oestrogen replacement in *women* who have undergone hysterectomy and oophorectomy (see Menopausal Hormone Replacement Therapy, p. 2307.1).

There has also been growing interest in the use of testosterone therapy in *healthy older men*, although there is limited evidence to prove a direct association between clinical changes and the natural decline of endogenous hormone concentrations with age.[9] This aspect of ageing is increasingly being described as the andropause, but the fall in testosterone concentrations is gradual, and not a rapid and significant decline of hormones with loss of fertility like that which occurs in the female menopause[9,10] (p. 2244.1); other terms such as partial androgen deficiency or late-onset hypogonadism have also been proposed.[9] Testosterone therapy has been studied in healthy older men with normal or low-normal serum-testosterone concentrations. Modest beneficial changes in body composition (increased lean body-mass and decreased fat-mass) have been reported, but many studies have found no associated improvement in muscle strength, mobility, or functional autonomy, or a reduced risk of falls. Results are also inconsistent or negative from studies measuring skeletal effects, sexual function, cognitive function, mood, and quality of life.[9] A meta-analysis[11] of 8 studies suggested that intramuscular testosterone might be more effective than transdermal administration for increasing lumbar bone mineral density. There are concerns about potential adverse effects of testosterone on the prostate (see Carcinogenicity, p. 2307.3) and the cardiovascular system, and high doses have been reported to cause or exacerbate sleep apnoea.[9,12] Although recommendations have been made for the use and monitoring of testosterone therapy in healthy older men with androgen deficiency,[12-14] many caution that until further clinical studies have been done it should only be used in those with confirmed hypogonadism.[9,10]

1. Gooren LJG, Bunck MCM. Androgen replacement therapy: present and future. *Drugs* 2004; **64**: 1861–91.
2. Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. *Clin Endocrinol (Oxf)* 2006; **65**: 275–81.
3. Bhasin S, *et al.* Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010; **95**: 2536–59. Also available at: http://www.endo-society.org/guidelines/final/upload/FINAL-Androgens-in-Men-Standalone.pdf (accessed 14/07/10)
4. Moorthy B, *et al.* Depot testosterone in boys with anorchia or gonadotrophin deficiency: effect on growth rate and adult height. *Arch Dis Child* 1991; **66**: 197–9.
5. Zacharin MR, Warne GL. Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets. *Arch Dis Child* 1997; **76**: 495–9.
6. Wang C, *et al.* Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. *Clin Endocrinol (Oxf)* 2001; **54**: 739–50.
7. Zacharin MR, *et al.* Bone mineral density outcomes following long-term treatment with subcutaneous testosterone pellet implants in male hypogonadism. *Clin Endocrinol (Oxf)* 2003; **58**: 691–5.
8. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004; **350**: 482–92.
9. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev* 2005; **26**: 833–76.

10. Juul A, Skakkebæk NE. Androgens and the ageing male. *Hum Reprod Update* 2002; 8: 423–33.
11. Tracz MJ, *et al.* Testosterone use in men and its effects on bone health: a systematic review and meta-analysis of randomized placebo-controlled trials. *J Clin Endocrinol Metab* 2006; 91: 2011–16.
12. Liu PY, *et al.* The rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. *J Clin Endocrinol Metab* 2004; 89: 4789–96.
13. Wald M, *et al.* Testosterone replacement therapy for older men. *J Androl* 2006; 27: 126–32.
14. Wang C, *et al.* ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Int J Impot Res* 2009; 21: 1–8. Also available at: http://www.nature.com/ijir/journal/v21/n1/abs/ijir200841a.html (accessed 11/11/09)

Lichen sclerosus. Topical androgens such as androstanolone and testosterone have been used to treat vulvar lichen sclerosus (p. 1685.2) in postmenopausal women.[1-4] However, virilisation can occur and a topical corticosteroid is generally preferred.[5]

1. Pasilin D. Treatment of lichen sclerosus with topical dihydrotestosterone. *Obstet Gynecol* 1991; 78: 1046–9.
2. Bracco GL, *et al.* Clinical and histologic effects of topical treatments of vulval lichen sclerosus: a critical evaluation. *J Reprod Med* 1993; 38: 37–40.
3. Pasilin D. Androgens in the topical treatment of lichen sclerosus. *Int J Dermatol* 1996; 35: 298–301.
4. Joura EA, *et al.* Short-term effects of topical testosterone in vulvar lichen sclerosus. *Obstet Gynecol* 1997; 89: 297–9.
5. 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)

Male contraception. In male contraceptive studies it was found that high-dose testosterone severely reduced sperm production.[1] In those in whom azoospermia was not induced there was oligozoospermia with remaining sperm having a markedly reduced fertilising capacity. In a multicentre study carried out by WHO[2] involving 271 healthy fertile men, weekly intramuscular injection of testosterone enantate 200 mg produced azoospermia in 157 men within 6 months. In a subsequent 12-month study of these azoospermic men, during which time testosterone enantate was the only contraceptive measure used, there was only 1 pregnancy. Spermatogenesis was re-established on withdrawal of testosterone. These findings have been confirmed in a larger study of the same regimen, which additionally assessed contraceptive efficacy in men who achieved oligozoospermia (less than 3×10^6/mL).[3] No pregnancies occurred in couples where the man was azoospermic. However, the pregnancy rate was 8.1 per 100-person-years in the subgroup of couples where the man was oligozoospermic. This rate is sixfold higher than is generally seen with hormonal contraceptives in women.[4] Both studies found that consistent azoospermia was achieved in a higher percentage of Asian men (95%) than Western men (70%).[4] Testosterone undecylate has also been studied as a longer-acting intramuscular injection. In a study[5] involving Chinese men, a loading dose of 1 g followed by monthly maintenance doses of 500 mg effectively and persistently suppressed spermatogenesis in about 95% of 296 men who had initially responded; pregnancy occurred in the partner of 1 of the 6 men with sperm rebound.

An alternative approach being investigated is the use of testosterone with a progestogen, which enhances the suppression of spermatogenesis and may allow lower doses of androgen to be used with fewer adverse effects. Progestogens under investigation include cyproterone, desogestrel, etonogestrel, levonorgestrel, medroxyprogesterone, and norethisterone.[6,7]

For a general discussion on choice of contraceptive method, including mention of male contraception, see p. 2232.3.

1. Matsumoto AM. Is high dosage testosterone an effective male contraceptive agent? *Fertil Steril* 1988; 50: 324–8.
2. WHO Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. *Lancet* 1990; 336: 955–9.
3. WHO Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertil Steril* 1996; 65: 821–9.
4. Anonymous. An androgen contraceptive for men: preliminary findings. *WHO Drug Inf* 1996; 10: 50–3.
5. Gu Y-Q, *et al.* A multicenter contraceptive efficacy study of injectable testosterone undecanoate in healthy Chinese men. *J Clin Endocrinol Metab* 2003; 88: 562–8.
6. Amory JK, *et al.* Drug insight: Recent advances in male hormonal contraception. *Nat Clin Pract Endocrinol Metab* 2006; 2: 32–41.
7. Grimes DA, *et al.* Steroid hormones for contraception in men. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 13/11/07).

Menopausal hormone replacement therapy. Menopause does not necessarily result in androgen deficiency in women, and androgen replacement is therefore not routinely required (see Menopausal Disorders, p. 2245.1). In the UK menopausal women may nonetheless sometimes be given implants of testosterone as an adjunct to menopausal HRT. In the USA, injectable preparations containing an androgen and an oestrogen have been available for the treatment of menopausal vasomotor symptoms, but there is conflicting opinion as to their usefulness, and further data are needed.[1] In Canada, a preparation containing estradiol and testosterone esters for intramuscular injection (*Climacteron; Sabex, Canad.*) was discontinued in 2005 because of concerns that testosterone is partially metabolised to oestrogen, which should be opposed by a progestogen in women with a uterus, and that there was no established dose of progestogen that could be recommended in this situation.[2] A study[3] in healthy postmenopausal women found that oral testosterone alone did not stimulate endometrial proliferation as estradiol did, and that it appeared to reduce the effect of estradiol when they were used together. However, therapy was given for only 3 months and long-term effects need further study.

Improvements in mood and libido have been reported when androgens were given to postmenopausal women with an established cause of androgen deficiency such as surgically induced menopause.[4] A systematic review of the addition of testosterone to postmenopausal HRT considered that there was some evidence of benefit on sexual function, but that studies varied too much to estimate the effect of any particular combination.[5] More recently, several placebo-controlled studies in women with surgically induced[8,9] or natural[10] menopause have reported improvements in sexual activity and desire with HRT plus transdermal testosterone. A product (*Intrinsa; Proctor and Gamble, UK*) was licensed for use in the UK for the treatment of hypoactive sexual desire disorder in women with surgically induced menopause who were also receiving oestrogen replacement therapy, but the FDA did not license it in the USA and expressed concern about the lack of data on long-term safety.[11] Subsequently, a 1-year study[12] found that transdermal testosterone, without an oestrogen, improved sexual function in postmenopausal women. The most commonly reported androgenic adverse effect was increased hair growth, but there were also a few cases of mild clitoral enlargement. Breast cancer was diagnosed in a few women; a causal relationship could not be established and further study is needed. The role of testosterone for sexual function in postmenopausal women continues to be evaluated.[13]

The Endocrine Society[14] has evaluated data on the use of testosterone in various groups of women, including those with menopausal symptoms, and advises that although there is some evidence for efficacy in selected populations, such as surgically menopausal women, it cannot be recommended for generalised use because of poorly-defined indications and a lack of evidence on long-term safety.

The use of transdermal testosterone, with oestrogen and progestogen replacement therapy, is also being investigated in young women with spontaneous premature ovarian failure.[15]

1. Abraham D, Carpenter PC. Issues concerning androgen replacement therapy in postmenopausal women. *Mayo Clin Proc* 1997; 72: 1051–5.
2. Sandoz Canada. Discontinuation of Climacteron Injection (estradiol dienanthate/estradiol benzoate and testosterone enanthate benzilic acid hydrazone injection in corn oil) (issued 23rd November, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/climacteron_hpc-cps-eng.pdf (accessed 22/08/08)
3. Zang H, *et al.* Effects of testosterone treatment on endometrial proliferation in postmenopausal women. *J Clin Endocrinol Metab* 2007; 92: 2169–75.
4. Arlt W. Androgen therapy in women. *Eur J Endocrinol* 2006; 154: 1–11.
5. Somboonporn W, *et al.* Testosterone for peri- and postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 13/11/07).
6. Shifren JL, *et al.* Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000; 343: 682–8.
7. Simon J, *et al.* Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005; 90: 5226–33.
8. Braunstein GD, *et al.* Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 2005; 165: 1582–9.
9. Buster JE, *et al.* Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005; 105: 944–52.
10. Shifren JL, *et al.* Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause* 2006; 13: 770–9.
11. Moynihan R. FDA panel rejects testosterone patch for women on safety grounds. *BMJ* 2004; 329: 1363.
12. Davis SR, *et al.* APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med* 2008; 359: 2005–17.
13. Krapf JM, Simon JA. The role of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. *Maturitas* 2009; 63: 213–19.
14. Wierman ME, *et al.* Androgen therapy in women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006; 91: 3697–3710. Also available at: http://www.endo-society.org/guidelines/final/upload/Androgens_in_Women_CG.pdf (accessed 22/08/08)
15. Kalantaridou SN, *et al.* A pilot study of an investigational testosterone transdermal patch system in young women with spontaneous premature ovarian failure. *J Clin Endocrinol Metab* 2005; 90: 6549–52.

Rheumatoid arthritis. A hypogonadal condition characterised by low serum-testosterone concentrations appears to be associated with at least the active stages of rheumatoid arthritis (p. 13.2) in men.[1] Clinical improvement and reductions in IgM rheumatoid factor concentration, tender joint count, and the daily dosage of NSAIDs required, were seen in a small study[1] of men with rheumatoid arthritis and low serum-testosterone concentrations given oral testosterone undecylate 40 mg three times daily for 6 months. Improvements in rheumatoid arthritis were also seen in 12 of 36 postmenopausal women treated with intramuscular testosterone propionate 50 mg plus a low dose of progesterone (2.5 mg) once every 2 weeks compared with 2 of 32 women given placebo.[2] However, a placebo-controlled study[3] in 30 men with normal serum-testosterone concentrations found no beneficial effect from intramuscular testosterone enantate on measures of disease activity.

1. Cutolo M, *et al.* Androgen replacement therapy in male patients with rheumatoid arthritis. *Arthritis Rheum* 1991; 34: 1–5.
2. Booij A, *et al.* Androgens as adjuvant treatment in postmenopausal female patients with rheumatoid arthritis. *Ann Rheum Dis* 1996; 55: 811–15.
3. Hall GM, *et al.* A randomized trial of testosterone therapy in males with rheumatoid arthritis. *Br J Rheumatol* 1996; 35: 568–73.

Adverse Effects

Testosterone and other androgens may give rise to adverse effects related to their androgenic or anabolic activities. These include increased retention of sodium and water, oedema, hypercalcaemia, and impaired glucose tolerance. Other effects include increased low-density-lipoprotein cholesterol, decreased high-density-lipoprotein cholesterol, increased haematocrit, and suppression of clotting factors. Androgens may cause headache, depression, irritability, aggression, and gastrointestinal disturbances including bleeding. It has been suggested that androgens may induce sleep apnoea in susceptible patients.

Abnormal liver function tests may occur and there have been reports of liver toxicity including jaundice and cholestatic hepatitis. There have also been reports of peliosis hepatis and hepatic tumours in patients given high doses over prolonged periods. These adverse hepatic effects have occurred mainly with the 17α-alkylated derivatives (e.g. methyltestosterone, stanozolol).

In men, large doses suppress spermatogenesis and cause testicular atrophy. Epididymitis and bladder irritability can occur. Priapism is a sign of excessive dosage and may occur especially in elderly males. Gynaecomastia may occur. Androgens may cause prostatic hyperplasia and accelerate the growth of malignant neoplasms of the prostate. Prostate specific antigen values can increase during testosterone therapy.

In women, the inhibitory action of androgens on the activity of the anterior pituitary results in the suppression of ovarian activity and menstruation. Continued use produces symptoms of virilism, such as hirsutism or male-pattern baldness, deepening of the voice, atrophy of the breasts and endometrial tissue, oily skin, acne, and hypertrophy of the clitoris. Virilisation may not be reversible, even after stopping therapy.

Large and repeated doses in early puberty may cause closure of the epiphyses and stop linear growth. Children may show virilisation: in boys there may be precocious sexual development with phallic enlargement and increased frequency of erection, and in girls, clitoral enlargement. Gynaecomastia may also occur in boys.

Masculinisation of the external genitalia of the female fetus may occur if androgens are given during pregnancy.

After transdermal application of testosterone, skin reactions may include irritation, erythema, allergic contact dermatitis, and sometimes burn-like lesions. Skin reactions are more common with patches that contain permeation enhancers.

The **anabolic steroids**, because they generally retain some androgenic activity, share the adverse effects of the androgens described above, but their virilising effects, especially in women, are usually less. There have been reports of adverse psychiatric effects in athletes taking large doses to try and improve performance. For adverse effects after misuse of anabolic steroids, see Abuse under Precautions, p. 2308.2.

Carcinogenicity. Testosterone therapy is used in healthy older men with low or low-normal serum-testosterone concentrations (see Hypogonadism, under Uses and Administration, p. 2306.3), but there is some concern about a possible associated increase in prostate cancer risk. This concern is based on the fact that, regardless of any treatment, the incidence of prostate cancer increases with age, that normal prostate growth is dependent on androgens, and that androgen deprivation causes regression of advanced prostate cancer.[1] However, the relationship between androgens and the onset of prostate cancer is far from clear. Some data show that low serum-testosterone can predict more aggressive high-grade tumours, with a higher likelihood of metastatic disease and poorer outcome.[1-3] Although there have been reports of prostate cancer developing in men who have been treated with testosterone,[4] considerable evidence, but from mostly small

clinical studies has, overall, not shown an increase in the risk of prostate cancer.[3,5] The effect of 6 months of testosterone enantate therapy on the prostate has been studied in 21 men (44 to 78 years old).[6] Although low serum-testosterone concentrations were normalised, there were no significant changes in androgen concentrations in prostate tissue, prostate volume, prostate specific antigen, or prostate cancer incidence. Further study of longer duration in larger numbers of men is needed to confirm the safety of this therapy.

In men with a history of prostate cancer, testosterone therapy for hypogonadism is generally contra-indicated because of the presumed risk of tumour recurrence. However, there are a small number of reports of testosterone being used safely after curative surgery, suggesting that testosterone therapy with close monitoring may be considered in such men with symptomatic hypogonadism.[3,7] There is even less data on the use of testosterone for hypogonadism in men who have been treated with radiotherapy with curative intent,[3] or with androgen ablation by gonadorelin analogue therapy. Testosterone has also been used for hypogonadism in a small number of men with high-grade intra-epithelial neoplasia, a precancerous lesion, without increasing the risk of cancer development.[7]

For reference to hepatic malignancies associated with androgens and anabolic steroids, see Effects on the Liver, below. Renal cell carcinoma has also been reported after their abuse (see under Precautions, below).

1. Raynaud J-P. Prostate cancer risk in testosterone-treated men. *J Steroid Biochem Mol Biol* 2006; 102: 261–6.
2. Barqawi A, Crawford ED. Testosterone replacement therapy and the risk of prostate cancer: is there a link? *Int J Impot Res* 2006; 18: 323–8.
3. Raynaud J-P. Testosterone deficiency syndrome: treatment and cancer risk. *J Steroid Biochem Mol Biol* 2009; 114: 96–105.
4. Brand TC, *et al.* Testosterone replacement therapy and prostate cancer: a word of caution. *Curr Urol Rep* 2007; 8: 185–9.
5. Gould DC, Kirby RS. Testosterone replacement therapy for late onset hypogonadism: what is the risk of inducing prostate cancer? *Prostate Cancer Prostatic Dis* 2006; 9: 14–18.
6. Marks LS, *et al.* Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006; 296: 2351–61.
7. Kaufman J. A rational approach to androgen therapy for hypogonadal men with prostate cancer. *Int J Impot Res* 2006; 18: 26–31.

Effects on the cardiovascular system. A cerebrovascular accident has been reported in a young man after the over-zealous self-administration of testosterone enantate intramuscularly for hypogonadism.[1] It was noted that thromboembolic complications are not generally recognised as adverse effects of androgen therapy although there is some experimental evidence that testosterone stimulates thrombus formation. A systematic review[2] found evidence concerning cardiovascular events in studies of testosterone given to men with low or normal testosterone concentrations to be of poor quality, but some data to suggest that alterations in plasma lipid concentrations and blood pressure were not significant.

1. Nagelberg SB, *et al.* Cerebrovascular accident associated with testosterone therapy in a 21-year-old hypogonadal man. *N Engl J Med* 1986; 314: 649–50.
2. Haddad RM, *et al.* Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007; 82: 29–39.

Effects on the liver. Hepatotoxicity, including elevations in liver enzymes, hepatic cholestasis and jaundice, and rarely peliosis hepatis and hepatic tumours, has occurred with androgens and anabolic steroids, particularly the 17α-alkylated derivatives. Prolonged treatment and high doses may be significant contributory factors. Tumours have included hepatocellular carcinomas, benign adenomas, and less commonly angiosarcomas and cholangiocarcinomas. Tumours and peliosis may regress on stopping therapy, but they can also progress to liver failure and death. Some reviews of the hepatic effects of androgens and anabolic steroids are cited below.[1-5] There has been a specific report of benign hepatic adenoma in a patient treated with testosterone enantate for 11 years,[6] and of hepatocellular carcinoma in a patient given testosterone enantate and methyltestosterone.[7] Further specific references may be found under individual drug monographs.

1. Bagheri SA, Boyer JL. Peliosis hepatis associated with androgenic-anabolic steroid therapy. *Ann Intern Med* 1974; 81: 610–18.
2. Ishak KG, Zimmerman HJ. Hepatotoxic effects of the anabolic/androgenic steroids. *Semin Liver Dis* 1987; 7: 230–6.
3. Sae KL, *et al.* Liver pathology associated with the use of anabolic-androgenic steroids. *Liver* 1992; 12: 73–9.
4. Touraine RL, *et al.* Hepatic tumours during androgen therapy in Fanconi anaemia. *Eur J Pediatr* 1993; 152: 691–3.
5. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; 77: 257–67.
6. Carrasco D, *et al.* Hepatic adenomata and androgen treatment. *Ann Intern Med* 1984; 100: 316.
7. Johnson FL, *et al.* Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 1972; ii: 1273–6.

Effects on sexual function. Priapism has occurred after the use of testosterone for the management of delayed puberty[1-4] or hypogonadism.[5-7]

1. Zeilssen PMJ, Stricker BHC. Severe priapism as a complication of testosterone substitution therapy. *Am J Med* 1988; 85: 273–4.
2. Ruch W, Jenny P. Priapism following testosterone administration for delayed male puberty. *Am J Med* 1989; 86: 256.
3. Madrid García FJ, *et al.* Priapismo secundario a la administración de testosterona en el tratamiento del retraso puberal. *Arch Esp Urol* 2001; 54: 703–5.
4. Arrigo T, *et al.* High-flow priapism in testosterone-treated boys with constitutional delay of growth and puberty may occur even when very low doses are used. *J Endocrinol Invest* 2005; 28: 390–1.
5. Zargooshi J. Priapism as a complication of high dose testosterone therapy in a man with hypogonadism. *J Urol (Baltimore)* 2000; 163: 907.
6. Shergill IS, *et al.* Testosterone induced priapism in Kallmann's syndrome. *J Urol (Baltimore)* 2003; 169: 1089.
7. Ichioka K, *et al.* Testosterone-induced priapism in Klinefelter syndrome. *Urology* 2006; 67: e17–e18.

Precautions

Testosterone and other androgens and anabolic steroids should be used cautiously in patients with cardiovascular disorders, renal or hepatic impairment, epilepsy, migraine, diabetes mellitus or other conditions that may be aggravated by the possible fluid retention or oedema caused. They should not be given to patients with hypercalcaemia or hypercalciuria, and should be used cautiously in conditions in which there is a risk of these developing such as skeletal metastases. The use of the 17α-alkylated derivatives, which are associated with an increased risk of hepatotoxicity, is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Hepatic function should be monitored during therapy.

In men, androgens and anabolic steroids should not be given to those with carcinoma of the breast or prostate (although in women they have been used in the treatment of certain breast carcinomas; see also Carcinogenicity, p. 2307.3, regarding the use of testosterone in men with a history of prostate cancer). The prostate should be examined regularly during treatment.

Androgens and anabolic steroids should not be given during pregnancy because of the risk of virilisation of the female fetus.

Androgens and anabolic steroids should be used with extreme care in children because of the masculinising effects and also because premature closure of the epiphyses may occur resulting in inhibited linear growth and small stature. Skeletal maturation should be monitored during therapy.

Patients using testosterone gels or topical solutions should take care to wash their hands after every application, and to cover the site with clothing once the preparation has dried. The area should also be washed thoroughly before skin-to-skin contact with another person. Inappropriate virilisation, advanced bone age, increased libido, and aggressive behaviour have been reported in children who have been inadvertently exposed to testosterone in this way.

Androgens and anabolic steroids may interfere with some clinical laboratory tests such as those for glucose tolerance and thyroid function.

Abuse. The adverse effects arising from the illicit use of androgens and anabolic steroids by athletes, often taken together at doses well in excess of those used therapeutically, have been discussed.[1-5] Such misuse is associated with potentially serious health risks. Effects have included abnormal liver function and hepatic neoplasms (see also Effects on the Liver, above), an atherogenic blood lipid profile and increased risk of cardiovascular disease, and reduced glucose tolerance. Hypogonadal states are commonly induced (azoospermia or oligospermia and testicular atrophy in men, and amenorrhoea or oligomenorrhoea in women). Gynaecomastia is relatively common in men, and virilisation in women. Psychiatric disturbances such as mania, hypomania, depression, aggression, and emotional lability, have been described. There is also some evidence that dependence associated with an acute withdrawal syndrome can occur. Rare reports include alterations in immune response, tendon damage, renal cell carcinoma, and peliosis hepatis.

There has been some dispute about the methods used to detect abuse of certain anabolic steroids in athletes. A study in healthy subjects has apparently confirmed endogenous production of small amounts of nandrolone metabolites;[6] several different factors might have an influence including genetics, intense exercise, trauma, and hypoglycaemic stress.[7]

1. Pärssinen M, Seppälä T. Steroid use and long-term health risks in former athletes. *Sports Med* 2002; 32: 83–94.
2. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med* 2004; 34: 513–54.
3. Maravelias C, *et al.* Adverse effects of anabolic steroids in athletes: a constant threat. *Toxicol Lett* 2005; 158: 167–75.
4. Trenton AJ, Currier GW. Behavioural manifestations of anabolic steroid use. *CNS Drugs* 2005; 19: 571–95.
5. Sjöqvist F, *et al.* Use of doping agents, particularly anabolic steroids, in sports and society. *Lancet* 2008; 371: 1872–82.
6. Reznik Y, *et al.* Urinary nandrolone metabolites of endogenous origin in man: a confirmation by output regulation under human chorionic gonadotropin stimulation. *J Clin Endocrinol Metab* 2001; 86: 146–50.
7. Kohler RMN, Lambert ML. Urine nandrolone metabolites: false positive doping test? *Br J Sports Med* 2002; 36: 325–9.

Breast feeding. It is unknown whether testosterone is distributed into breast milk, but it should be avoided in women who are breast feeding because of the theoretical potential androgenic effect on the infant. High doses of testosterone can suppress lactation.

Inadvertent transfer. A brief review[1] of the risks of inadvertent secondary exposure to testosterone gel used for male hormone replacement in women or children, with consequent virilisation or hyperandrogenism.

1. de Ronde W. Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies. *Hum Reprod* 2009; 24: 425–8.

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

A female patient with acute intermittent porphyria (p. 1556.1) who suffered from severe attacks premenstrually was successfully managed with subcutaneous implants of testosterone when suppression of the menstrual cycle with buserelin met with limited success.[2]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)
2. Savage MW, *et al.* Acute intermittent porphyria treated by testosterone implant. *Postgrad Med J* 1992; 68: 479–81.

Pregnancy. Reports of female fetal virilisation after maternal use of testosterone[1] or methyltestosterone[2] during pregnancy.

1. Reschini E, *et al.* Female pseudohermaphroditism due to maternal androgen administration: 25-year follow-up. *Lancet* 1985; i: 1226.
2. Dewhurst J, Gordon RR. Fertility following change of sex. *Lancet* 1984; ii: 1461.

Veterinary use. An FAO/WHO expert committee examining the risks from residue of veterinary drugs in foodstuffs established an acceptable daily intake for testosterone, but concluded that there would be no need to specify a numerical maximum residue limit for testosterone in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that, in the EU, the use of androgens in veterinary practice is restricted and their use as growth promotors is banned. In addition, the use of anabolic steroids is banned in animals intended for human consumption.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 09/07/08)

Interactions

Testosterone and other androgens and anabolic steroids have been reported to enhance the activity of various drugs, with resulting increases in toxicity. Drugs affected include ciclosporin (see p. 1955.1), levothyroxine (see p. 2342.2), and anticoagulants such as warfarin (see p. 1535.1). Resistance to the effects of neuromuscular blockers (p. 2033.2) has also been reported. As androgens and anabolic steroids can alter glucose metabolism, doses of insulin or oral antidiabetics may need adjustment.

Pharmacokinetics

Testosterone is absorbed from the gastrointestinal tract, the skin, and the oral mucosa. However, it undergoes extensive first-pass hepatic metabolism when given orally and is therefore usually given intramuscularly, subcutaneously, or transdermally. The basic molecule of testosterone has also been modified to produce orally active compounds and to extend the duration of action. Alkylation of the 17α position produces compounds that are more slowly metabolised by the liver, and hence may be given orally. Esterification of the 17β hydroxyl group increases lipid solubility and results in slower systemic absorption after intramuscular injection. The rate of absorption of the esters is related to the size of the ester group. The undecylate ester undergoes less complete inactivation after oral doses because of distribution into the lymphatic system. Testosterone esters are hydrolysed to testosterone after absorption.

Testosterone is about 80% bound to sex-hormone binding globulin. Derivatives of 19-nortestosterone and 17-α-methylated compounds have reduced binding to this globulin. The plasma half-life of testosterone is reported to range from about 10 to 100 minutes. It is largely metabolised in the liver via oxidation at the 17-OH group with the formation of androstenedione, which is further metabolised to the weakly androgenic androsterone and inactive etiocholanolone which are excreted in the urine mainly as glucuronides and sulfates. About 6% is excreted

unchanged in the faeces after undergoing enterohepatic recirculation. Testosterone is converted to the more active dihydrotestosterone in some target organs by 5α-reductase. 19-Nortestosterone derivatives appear to be less susceptible to this enzyme. Small amounts of testosterone are aromatised to form oestrogenic derivatives, particularly oestradiol. Compounds with a saturated A-ring, such as mesterolone, appear to be less likely to be aromatised to oestrogen.

References to the pharmacokinetics of subcutaneous testosterone pellets,[1] intramuscular depot injection,[2] scrotal[3,4] and non-scrotal[5-8] transdermal patches, gel,[9,10] and a buccal preparation,[11,12] are given below.

1. Handelsman DJ, *et al.* Pharmacokinetics and pharmacodynamics of testosterone pellets in man. *J Clin Endocrinol Metab* 1990; 71: 216–22.
2. Yassin AA, Haffejee M. Testosterone depot injection in male hypogonadism: a critical appraisal. *Clin Interv Aging* 2007; 2: 577–90.
3. Findlay JC, *et al.* Transdermal delivery of testosterone. *J Clin Endocrinol Metab* 1987; 64: 266–8.
4. Cunningham GR, *et al.* Testosterone replacement with transdermal therapeutic systems: physiological serum testosterone and elevated dihydrotestosterone levels. *JAMA* 1989; 261: 2525–30.
5. Meikle AW, *et al.* Pharmacokinetics and metabolism of a permeation-enhanced testosterone transdermal system in hypogonadal men: influence of application site. *J Clin Endocrinol Metab* 1996; 81: 1832–40.
6. Yu Z, *et al.* Transdermal testosterone administration in hypogonadal men: comparison of pharmacokinetics at different sites of application and at the first and fifth days of application. *J Clin Pharmacol* 1997; 37: 1129–38.
7. Dobs AS, *et al.* Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab* 1999; 84: 3469–78.
8. Singh AB, *et al.* Pharmacokinetics of a transdermal testosterone system in men with end stage renal disease receiving maintenance hemodialysis and healthy hypogonadal men. *J Clin Endocrinol Metab* 2001; 86: 2437–45.
9. Swerdloff RS, *et al.* Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab* 2000; 85: 4500–10.
10. Marbury T, *et al.* Evaluation of the pharmacokinetic profiles of the new testosterone topical gel formulation, Testim™, compared to AndroGel. *Biopharm Drug Dispos* 2003; 24: 115–20.
11. Korbonits M, *et al.* A comparison of a novel testosterone bioadhesive buccal system, Striant, with a testosterone adhesive patch in hypogonadal males. *J Clin Endocrinol Metab* 2004; 89: 2039–43.
12. Wang C, *et al.* New testosterone buccal system (Striant) delivers physiological testosterone levels: pharmacokinetics study in hypogonadal men. *J Clin Endocrinol Metab* 2004; 89: 3821–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Androlone; Androtag; Nebido; Sustanon 250; Testex; Testoviron Depot 100; Testoviron Depot 250; Undestor; *Austral.*: Andriol; Andro-Feme; Androderm; Primoteston Depot; Reandron; Sustanon 100†; Sustanon 250; Testogel; *Austria*: Andriol; Nebido; Testogel; *Belg.*: AndroGel; Itnogen; Nebido; Sustanon 250; Testim; Testocaps; *Braz.*: Androxon; Deposteron; Nebido; *Canad.*: Andriol; Androderm; AndroGel; Delatestryl; Testim; *Chile*: Actiser-T; Nebido; Primoniat Depot; Sustenan 250; Sustenan†; Testocaps; Testovital; *China*: Andriol (安特尔); Nuo Shi (诺仕); Si Te Long (思特珑); *Cz.*: Agovirin; AndroGel; Intrinsa†; Livensa†; Nebido; Sustanon; Testopatch†; Tostran†; Undestor; *Denm.*: Andriol; Nebido; Testim; Testogel; Testoviron Depot 250†; Tostran; *Fin.*: Nebido; Panteston; Sustanon 250; Testim; Testogel; Tostran; *Fr.*: AndroGel; Androtardyl; Fortigel; Intrinsa†; Nebido; Pantestone; Testopatch; *Ger.*: Andriol; Androtop; Intrinsa†; Nebido; Striant†; Testim; Testogel; Testopatch; Testotop; Testoviron Depot 250; Tostran; *Gr.*: Androderm; Andropatch; Nebido; Restandol; Testim; Testogel; Testopatch; Testoviron; Tostran; *Hong Kong*: Andriol; AndroGel; Nebido; Sustanon; Testoviron Depot; *Hung.*: Andriol; AndroGel; Nebido; Tostran; *India*: Andriol; Androfil; Aquaviron; Cernos; Nuvir; Sustanon 100; Sustanon 250; Testanon 25†; Testanon 50†; Testoviron Depot; *Indon.*: Andriol; Nebido; Sustanon 250; *Irl.*: AndroGel; Andropatch†; Intrinsa†; Livensa†; Nebido; Restandol; Striant†; Sustanon 100†; Sustanon 250†; Testim; Testogel; Tostran; *Israel*: AndroGel; Androxon; Nebido; Sustanon 250; Testomax; Testoviron Depot; *Ital.*: Andriol; AndroGel; Intrinsa†; Nebid; Striant; Sustanon; Testim; Testo-Enant; Testogel; Testopatch; Testovis; Tostrex; *Malaysia*: Andriol; Nebido; *Mex.*: Andriol; Lowtiyel; Nebido; Primoteston Depot; Sostenon; Testoprim-D; *Neth.*: Andriol; AndroGel; Intrinsa†; Livensa†; Nebido; Striant†; Sustanon 100; Sustanon 250; Testim; Testogel; Tostran; *Norw.*: Andriol; Atmos†; Nebido; Testim; Testogel; Tostran; *NZ*: Andriol; Androderm; Panteston; Primoteston Depot†; Reandron; Sustanon; *Philipp.*: Andriol; Nebido; *Pol.*: Androtop; Intrinsa†; Livensa†; Nebido; Omnadren; Testosteronum Prolongatum; Tostran; Undestor; *Port.*: Andriol; AndroGel; Intrinsa†; Livensa†; Nebido; Striant†; Testim; Testogel; Testopatch; Testoviron Depot; Tostran; *Rus.*: Andriol (Андриол); AndroGel (Андрогель); Nebido (Небидо); Omnadren (Омнадрен); Sustanon 250 (Сустанон 250); *S.Afr.*: Androxon; Depotrone; Nebido; Sustanon 250; *Singapore*: Andriol; AndroGel; Nebido; Sustanon 250; *Spain*: Intrinsa†; Itnogen; Numanis†; Reandron; Testex; Testim; Testogel; Testopatch; *Swed.*: Atmos†; Intrinsa†; Nebido; Testim; Testogel; Tostrex; Undestor; *Switz.*: Andriol; Nebido; Testogel; Testoviron Depot; Tostran; *Thai.*: Andriol; Cypionax; Depo-Test; Nebido; Test-Comp; Testolic; Testoviron Depot; *Turk.*: Nebido; Sustanon 250; Testogel; Virigen; *UK*: Andropatch†; Intrinsa†; Nebido; Restandol; Striant; Sustanon 100†; Sustanon 250; Testim; Testogel; Testosterone Implants; Tostran; Virormone; *Ukr.*: Andriol (Андриол ТК); AndroGel (Андрогель); Nebido (Небидо); Omnadren (Омнадрен); *USA*: Androderm; AndroGel; Axiron; Delatestryl; Fortesta; Striant; Testim; Testopel; *Venez.*: Andriol; AndroGel; Polysteron 250; Proviron Depot.

Multi-ingredient Preparations. *Braz.*: Durateston; Estandron P; Trinestril; *Chile*: Estandron Prolongado†; *Cz.*: Folivirin; *India*: Mixogen; *Ital.*: Pacovit; Testoviron; *Malaysia*: Sustanon 250; *Mex.*: Despamen; Sten; *Neth.*: Estandron Prolongatum†; *Port.*: Sustenon 250; *S.Afr.*: Mixogen†; Primodian Depot†; *Thai.*: Metharmon-F†; Primodian Depot†; *Turk.*: Estandron Prolan; *USA*: Depo-Testadiol†; Depotestogen†.

Pharmacopoeial Preparations

BP 2014: Testosterone Enantate Injection; Testosterone Implants; Testosterone Propionate Injection;

USP 36: Testosterone Cypionate Injection; Testosterone Enanthate Injection; Testosterone Injectable Suspension; Testosterone Propionate Injection.

Tetrahydrogestrinone ⊗

THG.

18a-Homo-pregna-4,9,11-trien-17β-ol-3-one.

$C_{21}H_{28}O_2$=312.5

CAS — 618903-56-3.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of tetrahydrogestrinone:

The Clear.

Profile

Tetrahydrogestrinone is a synthetic anabolic steroid that is structurally related to gestrinone (p. 2280.2) and trenbolone (p. 2310.2). It has been subject to abuse in sport.

Action. Tetrahydrogestrinone had androgenic and progestogenic activity in a yeast-based *in-vitro* bioassay study.[1] The anabolic and androgenic properties of tetrahydrogestrinone have also been studied in *animals*.[2-4]

1. Death AK, *et al.* Tetrahydrogestrinone is a potent androgen and progestin. *J Clin Endocrinol Metab* 2004; 89: 2498–2500.
2. Labrie F, *et al.* Tetrahydrogestrinone induces a genomic signature typical of a potent anabolic steroid. *J Endocrinol* 2005; 184: 427–33.
3. Jasuja R, *et al.* Tetrahydrogestrinone is an androgenic steroid that stimulates androgen receptor-mediated, myogenic differentiation in C3H10T1/2 multipotent mesenchymal cells and promotes muscle accretion in orchidectomized male rats. *Endocrinology* 2005; 146: 4472–8.
4. Priedel A, *et al.* Tetrahydrogestrinone is a potent but unselective binding steroid and affects glucocorticoid signalling in the liver. *Toxicol Lett* 2006; 164: 16–23.

Tibolone (BAN, USAN, rINN) ⊗

7α-Methylnorethynodrel; Org-OD-14; Tibolon; Tibolona; Tibolonii; Tibolonum; Тиболон.

17β-Hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one.

$C_{21}H_{28}O_2$=312.5

CAS — 5630-53-5.

ATC — G03CX01.

ATC Vet — QG03CX01.

UNII — FF9X0205V2.

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

Ph. Eur. 8: (Tibolone). A white or almost white, crystalline powder or crystals. It exhibits polymorphism. Practically insoluble in water; soluble in acetone and in methyl alcohol. Store at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Tibolone is a steroid derived from noretynodrel that has oestrogenic, progestogenic, and weak androgenic properties. It is used as menopausal HRT (below) for oestrogen deficiency symptoms, including vasomotor symptoms, in postmenopausal women. Tibolone may also be used in the prevention of postmenopausal osteoporosis in women at high risk of fracture who cannot be treated with other therapy. The usual oral dose is 2.5 mg daily in a continuous regimen. Tibolone should not be started for at least 12 months after the last menstrual period of a natural menopause, but may be started immediately in women who have undergone a surgical menopause or who are being treated with a gonadorelin analogue. Unlike oestrogen-based HRT, a progestogen is not added to tibolone therapy for women with an intact uterus.

In women with a uterus who are transferring from an oestrogen-only form of HRT to tibolone, it is suggested that a withdrawal bleed be induced with a progestogen before starting tibolone, and in those transferring from a cyclical combined HRT, tibolone should be started the day after finishing a full cycle. Women taking continuous combined HRT can be transferred to tibolone at any time.

'Add-back' therapy. Tibolone reduces the vasomotor symptoms and bone loss caused by gonadorelin analogues, without impairing their efficacy in the treatment of endometriosis[1,2] (p. 2264.1) and fibroids[3] (p. 2281.2). Tibolone also reduced vasomotor symptoms in a short-term study of women being treated with leuprorelin for premenstrual syndrome[4] (p. 2272.3).

1. Lindsay PC, *et al.* The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). *Fertil Steril* 1996; 65: 342–8.
2. Taskin O, *et al.* Effectiveness of tibolone on hypoestrogenic symptoms induced by goserelin treatment in patients with endometriosis. *Fertil Steril* 1997; 67: 40–5.
3. Palomba S, *et al.* A clinical trial of the effects of tibolone administered with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata. *Fertil Steril* 1998; 70: 111–18.
4. Di Carlo C, *et al.* Use of leuprolide acetate plus tibolone in the treatment of severe premenstrual syndrome. *Fertil Steril* 2001; 75: 380–4.

Menopausal disorders. The oestrogenic effects of tibolone make it effective in the management of menopausal disorders (p. 2245.1) such as vasomotor symptoms and vaginal atrophy. It may also be used for the prevention of postmenopausal bone loss, and there is some evidence that it may be useful for treating postmenopausal osteoporosis and reducing fracture risk. The progestogenic effects of tibolone are thought to be sufficient to prevent endometrial proliferation, so that, unlike the oestrogens that are generally used for menopausal HRT (p. 2244.2), a progestogen is not added to tibolone therapy for women with an intact uterus.

Reviews.

1. Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. *J Clin Endocrinol Metab* 2002; 87: 16–23.
2. Swegle JM, Kelly MW. Tibolone: a unique version of hormone replacement therapy. *Ann Pharmacother* 2004; 38: 874–81.
3. Kenemans P, Speroff L. Tibolone: clinical recommendations and practical guidelines: a report of the International Tibolone Consensus Group. *Maturitas* 2005; 51: 21–8.
4. Ettinger B. Tibolone for prevention and treatment of postmenopausal osteoporosis. *Maturitas* 2007; 57: 35–8.

Adverse Effects

Irregular vaginal bleeding or spotting may occur with tibolone, mainly during the first few months of treatment; unlike cyclical, but similar to continuous, combination HRT (p. 2246.3), tibolone does not produce regular withdrawal bleeding. Other effects on the genital tract may include leucorrhoea, pruritus, candidiasis, and vaginitis. Other adverse effects have included breast pain, weight gain, oedema, dizziness, skin reactions, headache, migraine, visual disturbances, gastrointestinal disturbances, hypertrichosis, altered liver function, depression, and arthralgia or myalgia.

Incidence of adverse effects. In 1994, the UK CSM had received reports of 2796 suspected adverse reactions with tibolone over 3 years, out of about 666 000 prescriptions.[1] The commonest reported effects were headache, dizziness, nausea, rash, itching, and weight gain. Vaginal bleeding appeared to occur in about 8 to 9% of recipients. There had also been 52 reports of migraine, 4 of exacerbation of migraine, and 49 reports of visual disturbances, some suggestive of migraine.

1. CSM/MCA. Tibolone (Livial). *Current Problems* 1994; 20: 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 18/08/08)

Carcinogenicity. *BREAST.* The large cohort Million Women study[1] examined breast cancer incidence and mortality in relation to HRT use. After an average follow-up of 2.6 years for incidence, and 4.1 years for mortality, data were available for a group of 18 186 women who had used tibolone. There were 184 cases of invasive breast cancer equating to an overall risk of 1.45 (95% confidence interval 1.25 to 1.68) relative to women who had never used HRT. This was between the relative risks calculated for oestrogen-only HRT (1.30) and combined HRT (2.00). The risk was raised for current but not past use of tibolone, and increased with total duration of use.

For comment on the risk of recurrence in women with a history of breast cancer see Malignant Neoplasms under Precautions, p. 2310.1.

1. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419–27. Correction. *ibid.*: 1160.

ENDOMETRIUM. Endometrial hyperplasia and endometrial carcinoma have been rarely reported after investigation of uterine bleeding in women receiving tibolone therapy,[1-3] as has exacerbation of adenomyosis.[4] Some of these women had previously received oestrogens.

A cohort and nested case-control study[5] found that tibolone might have been associated with an increased risk of endometrial cancer compared with conventional forms of combined HRT, but the data were weak and might have been affected by bias and uncontrolled confounding factors. The large cohort Million Women Study[6] of HRT included a

group of 28 028 who had used tibolone for an average of about 3 years. The risk of endometrial cancer was increased to 1.79 (95% confidence interval 1.43 to 2.25) in those who had used tibolone, compared with women who had never used HRT, and the risk was higher with more than 3 years of use compared with shorter durations. In contrast, a smaller randomised study[7] comparing tibolone with combined HRT recorded no cases of endometrial hyperplasia or carcinoma in 1317 women given tibolone for up to 2 years.

1. von Dadelszen P, *et al.* Endometrial hyperplasia and adenocarcinoma during tibolone (Livial) therapy. *Br J Obstet Gynaecol* 1994; **101**: 158–61.
2. Ginsburg J, Prelevic GM. Cause of vaginal bleeding in postmenopausal women taking tibolone. *Maturitas* 1996; **24**: 107–10.
3. Yazigi R, *et al.* Carcinoma of the endometrium in patients treated with tibolone. *Gynecol Oncol* 2004; **93**: 568–70.
4. Prys Davies A, Oram D. Exacerbation of adenomyosis in a postmenopausal woman taking tibolone associated with an elevation in serum CA 125. *Br J Obstet Gynaecol* 1994; **101**: 632–3.
5. de Vries CS, *et al.* Tibolone and endometrial cancer: a cohort and nested case-control study in the UK. *Drug Safety* 2005; **28**: 241–9.
6. Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005; **365**: 1543–51.
7. Archer DF, *et al.* Endometrial effects of tibolone. *J Clin Endocrinol Metab* 2007; **92**: 911–18.

Effects on the cardiovascular system. A study[1] of tibolone in the treatment of osteoporosis in postmenopausal women, aged between 60 and 85 years found that although it reduced the risk of fracture, breast cancer, and possibly colon cancer, there was an increased risk of stroke. The authors therefore concluded that tibolone should not be used in elderly women and women with risk factors for stroke.

1. Cummings SR, *et al.* LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008; **359**: 697–708.

Precautions

Tibolone is contra-indicated in women with breast cancer or oestrogen-dependent tumours, cardiovascular or cerebrovascular disorders including arterial or venous thromboembolism, or a history of these conditions, undiagnosed vaginal bleeding, untreated endometrial hyperplasia, and acute liver disorders. It should not be given to pregnant or breast-feeding women and is not intended for use in premenopausal women, except those being treated with a gonadorelin analogue.

Use of tibolone within 12 months of a natural menopause is not recommended because irregular vaginal bleeding is likely. Breakthrough bleeding and spotting may occur in the first few months of therapy, but should be investigated if it persists beyond 6 months, starts after that time, or continues after tibolone has been stopped. Missing a dose may increase the likelihood of bleeding and spotting.

Care should be taken when giving tibolone to patients with uterine fibroids, endometriosis, liver disease, gallstones, disorders that may be exacerbated by fluid retention such as cardiac or renal dysfunction, hypertension, epilepsy, or migraine, or with a history of these conditions. It should also be given with caution to patients with dyslipidaemia or diabetes mellitus. Patients with risk factors for thromboembolic disorders or oestrogen-dependent tumours, or a history of endometrial hyperplasia, should be closely monitored. Tibolone should be stopped if there are signs of thromboembolism, a significant increase in blood pressure, new onset of migraine-type headache, or if abnormal liver function tests or cholestatic jaundice occur. Consideration should be given to stopping tibolone 4 to 6 weeks before elective surgery when prolonged immobilisation after surgery is likely.

Malignant neoplasms. Licensed product information contra-indicates the use of tibolone in women with oestrogen-dependent tumours, as well as those with a history of breast cancer. Previously it had been suggested that, because of a less oestrogenic effect on breast tissue, tibolone might be a suitable alternative to oestrogen-based HRT for women with a history of breast cancer and there have been a few reports of its use for menopausal symptoms in such patients. An observational study[1] and a case-control study[2] of women who had been treated for breast cancer found no evidence that tumour recurrence was higher in those subsequently given tibolone than in those who were not. Case-control studies also suggested that tibolone did not increase the risk of recurrence of treated endometrial[3] or ovarian[4] cancers. Although promising, these data were limited and further studies were needed to confirm the safety of tibolone in these groups of patients, particularly as there was some evidence[5] that in UK general practice it may have been prescribed preferentially to women at increased risk of breast and endometrial cancers, including women with a history of breast cancer. The LIBERATE study[6] was aimed at testing whether tibolone did not increase the risk of breast cancer recurrence in postmenopausal women who had been treated surgically, many of whom were receiving adjuvant therapy. The study was stopped early, based on an interim safety assessment. Final results showed that after a median follow-up of about 3 years, there was an increased risk of cancer recurrence in those given tibolone, compared with placebo.

For reports of the incidence of breast and endometrial cancers in women given tibolone, see Carcinogenicity, p. 2309.3.

1. Dimitrakakis C, *et al.* Clinical effects of tibolone in postmenopausal women after 5 years of tamoxifen therapy for breast cancer. *Climacteric* 2005; **8**: 342–51.
2. Gountiounis M, *et al.* Tibolone therapy in breast cancer survivors: a retrospective study. *J Obstet Gynaecol Res* 2007; **33**: 68–73.
3. Lee K-B, *et al.* Endometrial cancer patients and tibolone: a matched case-control study. *Maturitas* 2006; **55**: 264–9.
4. Lee K-B, *et al.* The safety of tibolone in epithelial ovarian cancer patients. *Maturitas* 2006; **55**: 156–61.
5. Velthuis-te Wierik EJM, *et al.* Preferential prescribing of tibolone and combined estrogen plus progestogen therapy in postmenopausal women. *Menopause* 2007; **14**: 518–27.
6. Kenemans P, *et al.* LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol* 2009; **10**: 135–46.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tibolone 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 06/10/11)

Interactions

Compounds that induce liver enzymes, such as phenytoin, carbamazepine, and rifampicin, might theoretically enhance the metabolism of tibolone and thus reduce its activity.

For reference to the effect of tibolone on the activity of oral anticoagulants, see Sex Hormones under Warfarin, p. 1535.1.

Pharmacokinetics

Tibolone is rapidly and extensively absorbed after oral doses and quickly metabolised into three active metabolites, two of which have mainly oestrogenic activity while the third, like the parent compound, has progestogenic and androgenic activity. Peak concentrations of tibolone and its metabolites occur after about 1 to 1.5 hours, and the two main metabolites have an elimination half-life of about 7 hours. Metabolites are excreted in the bile and eliminated in the faeces. About 30% of a dose is excreted in the urine.

References.

1. Timmer CJ, Doorstam DP. Effect of renal impairment on the pharmacokinetics of a single oral dose of tibolone 2.5 mg in early postmenopausal women. *Pharmacotherapy* 2002; **22**: 148–53.
2. Timmer CJ, Huisman JA. Effect of a standardized meal on the bioavailability of a single oral dose of tibolone 2.5 mg in healthy postmenopausal women. *Pharmacotherapy* 2002; **22**: 310–15.
3. Timmer CJ, *et al.* Pharmacokinetics of tibolone in early and late postmenopausal women. *Br J Clin Pharmacol* 2002; **54**: 101–6.
4. Verheul HAM, *et al.* Pharmacokinetic parameters of sulfated tibolone metabolites in postmenopausal women after single and multiple doses of tibolone. *Clin Pharmacol Ther* 2007; **81**: 573–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cervictal; Climalona†; Climatix; Discretal; Paraclim; Senalina; Tibodim; Tibofem; Tiro-varina; Todine; *Austral.*: Livial; Xyvion; *Austria*: Liviel; *Belg.*: Heria; Livial; *Braz.*: Klimater; Libiam; Livial; Livolon; Reductim; Tibial; *Chile*: Climafen; Lirex; Livial; Plenovid†; Tinox; Tobe; *China*: Livial (利维爱); Qi Luo Shu (绣罗淑); *Cz.*: Ladybon; Livial; Tibolvivax; *Denm.*: Livial; *Fin.*: Livial; *Fr.*: Livial; *Ger.*: Liviella; *Gr.*: Livial; *Hong Kong*: Livial; *Hung.*: Livial; *India*: Livial; Maxtib; Tibolem; Tibomax; *Indon.*: Livial; *Irl.*: Livial; *Israel*: Livial; *Ital.*: Livial; *Malaysia*: Livial; *Mex.*: Bontil; Lisertil; Livial; Sintemel; *Neth.*: Livial; *Norw.*: Livial; *NZ*: Livial; *Philipp.*: Livial; Menorest; *Pol.*: Ladybon; Livial; *Port.*: Clitax; Goldar; Livial; Ulcinil; *Rus.*: Ladybon (Ледибон); Livial (Ливиал); *S. Afr.*: Livifem; *Singapore*: Livial; *Spain*: Boltin; *Swed.*: Livial; *Switz.*: Livial; *Thai.*: Livial; *Turk.*: Livial; *UK*: Livial; *Ukr.*: Livial (Ливиал); *Venez.*: Femsel; Fomene; Livial; Tinox.

Pharmacopoeial Preparations
BP 2014: Tibolone Tablets.

Trenbolone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de trenbolona; RU-1697; Trenbolona, acetato de; Trenbolone, Acétate de; Trenboloni Acetas; Trienbolone Acetate; Тренболона Ацетат.

17β-Hydroxyestra-4,9,11-trien-3-one acetate.

$C_{20}H_{24}O_3$=312.4

CAS — 10161-33-8 (trenbolone); 10161-34-9 (trenbolone acetate).

UNII — RUD5Y4SV0S.

Pharmacopoeias. In *US*, for veterinary use only.

USP 36: (Trenbolone Acetate). Store in airtight containers at a temperature of 2 degrees to 8 degrees.

Profile

Trenbolone acetate has been used as an anabolic agent in veterinary practice. The hexahydrobenzylcarbonate has also been used for its anabolic properties.

WHO specifies an acceptable daily intake of trenbolone acetate as a residue in foods, and recommends maximum residue limits in various animal tissues.[1] However, it should be noted that, in the EU the use of trenbolone acetate and other anabolic steroids is restricted to certain therapeutic indications in non-food producing animals and their use as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: thirty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 788* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_788.pdf (accessed 13/11/07)

Trimegestone *(BAN, USAN, rINN)*

RU-27987; Trimegeston; Trimegestona; Trimégestone; Trimegestoni; Trimegestonum; Тримегестон.

17β-(*S*)-Lactoyl-17-methylestra-4,9-dien-3-one; 17β-[(*S*)-2-Hydroxypropionyl]-17α-methylestra-4,9-dien-3-one.

$C_{22}H_{30}O_3$=342.5

CAS — 74513-62-5.

UNII — 4658K0H08W.

Profile

Trimegestone is a progestogen (see Progesterone, p. 2300.2) used as the progestogenic component of menopausal HRT (see p. 2244.1). It is given orally in daily doses of 250 or 500 micrograms in a cyclical regimen, or 125 micrograms in a continuous regimen. Trimegestone is also under investigation as a component of a combined oral contraceptive.

Reviews.

1. Grubb G, *et al.* Clinical experience with trimegestone as a new progestin in HRT. *Steroids* 2003; **68**: 921–6.
2. Sitruk-Ware R, *et al.* Preclinical and clinical properties of trimegestone: a potent and selective progestin. *Gynecol Endocrinol* 2007; **23**: 310–19.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trimegestone and oestrogen combinations 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 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Totelle Ciclico; Totelle Continuo; *Braz.*: Totelle Ciclo; Totelle; *Chile*: Ginotex; Lovelle Ciclico; Lovelle Continuo; Totelle Ciclico; Totelle Continuo; *Mex.* Totelle Continuo; Totelle Secuencial; *Venez.*: Totelle Ciclico Totelle Continuo.

Triptorelin *(BAN, USAN, rINN)* ⊗

AY-25650; BIM-21003; BN-52014; CL-118532; [6-D-Tryptophan] luteinising hormone-releasing factor; Triptorelina; Triptoreline; Triptoréline; Triptorelinum; D-Trp^6-LHRH; Трипторелин.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide.

$C_{64}H_{82}N_{18}O_{13}$=1311.5

CAS — 57773-63-4.

ATC — L02AE04.

ATC Vet — QL02AE04.

UNII — 9081Y98W2V.

Triptorelin Acetate *(BANM, rINNM)* ⊗

Acetato de triptorelina; Triptorelíniasetaatti; Triptorelin Asetat; Triptorelina, acetato de; Triptorelinacetat; Triptoréline, Acétate de; Triptorelini Acetas; Трипторелина Ацетат.

$C_{64}H_{82}N_{18}O_{13}.C_2H_4O_2$=1371.5

CAS — 140194-24-7.

ATC — L02AE04.

ATC Vet — QL02AE04.

UNII — 43OFW291R9.

Triptorelin Diacetate *(BANM, rINNM)* ⊗

Diacetato de triptorelina; Triptoréline, Diacetate de; Triptorelini Diacetas; Трипторелина Диацетат.

$C_{64}H_{82}N_{18}O_{13}.2C_2H_4O_2$=1431.6

CAS — 105581-02-0.

ATC — L02AE04.
ATC Vet — QL02AE04.

Triptorelin Embonate (BANM, rINNM) ⊗

Embonato de triptorelina; Triptorelin Pamoate (USAN); Triptorelinae embonatum; Triptoréline, Embonate de; Triptorelin Embonas; Трипторелина Эмбонат.
$C_{64}H_{82}N_{18}O_{13}$,$C_{23}H_{16}O_6$=1699.8
CAS — 124508-66-3.
ATC — L02AE04.
ATC Vet — QL02AE04.
UNII — 08AN7WA2G0.

Uses and Administration

Triptorelin is an analogue of gonadorelin (p. 2280.3) with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, deviant sexual behaviour in men, central precocious puberty, and in the management of endometriosis, female infertility, and uterine fibroids. Triptorelin may be given as the base, acetate, diacetate, or embonate, although for some preparations stated to contain the acetate or diacetate it is not always clear which has actually been used. Doses are usually given in terms of the base, and the following are each equivalent to about 1 mg of triptorelin:

- triptorelin acetate, 1.05 mg
- triptorelin diacetate, 1.09 mg
- triptorelin embonate, 1.30 mg

Triptorelin is given as a daily subcutaneous injection, or as an intramuscular or subcutaneous depot preparation lasting a month or longer.

In the palliative treatment of advanced **prostate cancer**, a dose equivalent to triptorelin 3 or 3.75 mg is given intramuscularly as a depot preparation every 4 weeks; the first dose may be preceded by 100 micrograms daily for 7 days by subcutaneous injection. In some countries, depot preparations containing 3.75 mg may be given subcutaneously instead. A longer-acting depot preparation that contains the equivalent of triptorelin 11.25 mg is given once every 12 to 13 weeks; a depot supplying the equivalent of 22.5 mg every 24 weeks is also available in some countries. Some countries also allow use of depot doses of 3 mg once every 4 weeks or 11.25 mg once every 12 to 13 weeks for medical therapy in locally advanced disease. An anti-androgen such as cyproterone acetate may be given for several days before beginning therapy with triptorelin and continued for about 3 weeks to avoid the risk of a disease flare.

An 11.25-mg intramuscular depot preparation, given every 12 weeks, may be used in the management of **deviant sexual behaviour** in men. The addition of an anti-androgen should be considered when starting therapy, to counteract the initial rise in serum-testosterone concentrations. Similarly, the addition of an anti-androgen should be considered before stopping triptorelin because of a risk of increased sensitivity to restored testosterone.

Similar doses of the 3- or 3.75-mg depot preparations may be given for up to 6 months in the management of **endometriosis** or **uterine fibroids**, with treatment begun during the first 5 days of the menstrual cycle. The 11.25-mg depot may be used as an alternative for endometriosis. In the management of female infertility doses of 100 micrograms subcutaneously daily, with gonadotrophins, have been recommended from the second day of the menstrual cycle for about 10 to 12 days.

Administration in children. Triptorelin may be used in the management of central precocious puberty and has been used in the diagnosis of delayed puberty. It has also been tried in the treatment of growth retardation (see below).

Diagnosis of hypothalamic and pituitary dysfunction. Gonadorelin analogues have been used in the diagnosis of delayed puberty (p. 2252.1). Triptorelin has been used in boys to differentiate gonadotrophin deficiency from constitutional delayed puberty,[1,2] although one study[3] found it to be less accurate than a test using human chorionic gonadotrophin.

1. Zamboni G, *et al.* Use of the gonadotropin-releasing hormone agonist triptorelin in the diagnosis of delayed puberty in boys. *J Pediatr* 1995; **126:** 756–8.
2. Kauschansky A, *et al.* Use of GnRH agonist and human chorionic gonadotrophin tests for differentiating constitutional delayed puberty from gonadotrophin deficiency in boys. *Clin Endocrinol (Oxf)* 2002; **56:** 603–7.
3. Degros V, *et al.* The human chorionic gonadotropin test is more powerful than the gonadotropin-releasing hormone agonist test to discriminate male isolated hypogonadotropic hypogonadism from constitutional delayed puberty. *Eur J Endocrinol* 2003; **149:** 23–9.

Disturbed behaviour. Combined therapy with triptorelin, which suppressed testosterone secretion by inhibiting the pituitary-gonadal axis, and supportive psychotherapy, has been tried in the treatment of men with paraphilias (see p. 1030.2): a reduction in abnormal sexual thoughts and behaviours has been reported, although the study was uncontrolled.[1]

1. Rösler A, Witztum E. Treatment of men with paraphilia with a long-acting analogue of gonadotropin-releasing hormone. *N Engl J Med* 1998; **338:** 416–22.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p. 2264.1), but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References.

1. Lindsay PC, *et al.* The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). *Fertil Steril* 1996; **65:** 342–8.
2. Bergqvist A, *et al.* Effects of triptorelin versus placebo on the symptoms of endometriosis. *Fertil Steril* 1998; **69:** 702–8.
3. Donnez J, *et al.* Equivalence of the 3-month and 28-day formulations of triptorelin with regard to achievement and maintenance of medical castration in women with endometriosis. *Fertil Steril* 2004; **81:** 297–304.
4. Wong AY, Tang L. An open and randomized study comparing the efficacy of standard danazol and modified triptorelin regimens for postoperative disease management of moderate to severe endometriosis. *Fertil Steril* 2004; **81:** 1522–7.
5. Loverro G, *et al.* A randomized study comparing triptorelin or expectant management following conservative laparoscopic surgery for symptomatic stage III-IV endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2008; **136:** 194–8.

Fibroids. Gonadorelin analogues have been used as an alternative to surgery in the treatment of uterine fibroids (see p. 2281.2), despite some concern that this may complicate the diagnosis of malignancy.

References to the use of triptorelin.

1. van Leusden HA. Symptom-free interval after triptorelin treatment of uterine fibroids: long-term results. *Gynecol Endocrinol* 1992; **6:** 189–98.
2. Golan A, *et al.* Pre-operative gonadotrophin-releasing hormone agonist treatment in surgery for uterine leiomyomata. *Hum Reprod* 1993; **8:** 450–2.
3. Broekmans FJ, *et al.* Two-step gonadotropin-releasing hormone agonist treatment of uterine leiomyomas: standard-dose therapy followed by reduced-dose therapy. *Am J Obstet Gynecol* 1996; **175:** 1208–16.
4. Vercellini P, *et al.* Treatment with a gonadotrophin releasing hormone agonist before hysterectomy for leiomyomas: results of a multicentre, randomised controlled trial. *Br J Obstet Gynaecol* 1998; **105:** 1148–54.
5. Seracchioli R, *et al.* GnRH agonist treatment before total laparoscopic hysterectomy for large uteri. *J Am Assoc Gynecol Laparosc* 2003; **10:** 316–19.

Growth retardation. As discussed on p. 1918.3 gonadorelin analogues have been given with growth hormone to short girls without growth hormone deficiency, in an attempt to delay puberty and bone maturation and thus maximise the final height achieved. Use in growth hormone-deficient children has also been investigated. However, there is some doubt about the extent of benefit, and in any case the concept of such treatment in children who are not clinically deficient in growth hormone is controversial, and some authorities do not consider it appropriate.

References to the use of triptorelin.

1. Saggese G, *et al.* Combination treatment with growth hormone and gonadotropin-releasing hormone analogs in short normal girls. *J Pediatr* 1995; **126:** 468–73.
2. Saggese G, *et al.* The effect of administering gonadotropin-releasing hormone agonist with recombinant-human growth hormone (GH) on the final height of girls with isolated GH deficiency: results from a controlled study. *J Clin Endocrinol Metab* 2001; **86:** 1900–4.
3. Kamp GA, *et al.* A randomized controlled trial of three years growth hormone and gonadotropin-releasing hormone agonist treatment in children with idiopathic short stature and intrauterine growth retardation. *J Clin Endocrinol Metab* 2001; **86:** 2969–75.
4. Tauber M, *et al.* Can some growth hormone (GH)-deficient children benefit from combined therapy with gonadotropin-releasing hormone analogs and GH? Results of a retrospective study. *J Clin Endocrinol Metab* 2003; **88:** 1179–83.

Infertility. Gonadorelin analogues are used in the management of infertility related to hypogonadotrophic hypogonadism in both men and women. For a discussion of infertility and its management, including the role of gonadorelin analogues, see p. 2253.1.

Malignant neoplasms. Triptorelin, like other gonadorelin analogues, may be used in the production of androgen blockade in patients with prostate cancer (p. 712.3).

References.

1. Klippel KF, *et al.* Wirksamkeit und Verträglichkeit von 2 Applikationsformen (s.c. und i.m.) von Decapeptyl Depot bei Patienten mit fortgeschrittenem Prostatakarzinom. *Urologe* 1999; **38:** 270–5.
2. Heyns CF, *et al.* Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. *BJU Int* 2003; **92:** 226–31.
3. Botto H, *et al.* Etude randomisée multicentrique comparant la castration médicale par triptoréline à la castration chirurgicale dans le traitement du cancer de la prostate localement avancé ou métastatique. *Prog Urol* 2007; **17:** 235–9.
4. Lundström EA, *et al.* Triptorelin 6-month formulation in the management of patients with locally advanced and metastatic prostate cancer: an open-label, non-comparative, multicentre, phase III study. *Clin Drug Investig* 2009; **29:** 757–65.
5. Keating GM. Triptorelin embonate (6-month formulation). *Drugs* 2010; **70:** 347–53.

Porphyria. Triptorelin has been used successfully to suppress premenstrual exacerbations of acute intermittent porphyria (p. 1556.1), in doses of 3.75 mg by intramuscular depot injection given monthly.[1,2] To reduce the risk of osteoporosis, 'add-back' therapy with topical oestrogen and oral calcium was used in one case,[1] and tibolone in another.[2]

1. De Block CEM, *et al.* Premenstrual attacks of acute intermittent porphyria: hormonal and metabolic aspects – a case report. *Eur J Endocrinol* 1999; **141:** 50–4.
2. Castelo-Branco C, *et al.* Use of gonadotropin-releasing hormone analog with tibolone to prevent cyclic attacks of acute intermittent porphyria. *Metabolism* 2001; **50:** 995–6.

Precocious puberty. The gonadorelin analogues have largely replaced other treatments in the management of central precocious puberty (p. 2254.1). A dose equivalent to triptorelin 50 micrograms/kg, from a 3-mg depot preparation, may be given intramuscularly every 4 weeks. Alternatively, using a 3.75-mg preparation, doses of 1.875 mg for children weighing less than 20 kg, 2.5 mg for children of 20 to 30 kg, or 3.75 mg for children of more than 30 kg, may be given intramuscularly or subcutaneously. The first 3 doses should be given at 14-day intervals, with further doses given every 4 weeks; this may be increased to once every 3 weeks if necessary. A longer acting 11.25-mg depot preparation, given intramuscularly once every 3 months, is another alternative.

References to the use of triptorelin.

1. Oostdijk W, *et al.* Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. *Arch Dis Child* 1996; **75:** 292–7.
2. Cassio A, *et al.* Randomised trial of LHRH analogue treatment on final height in girls with onset of puberty aged 7.5—8.5 years. *Arch Dis Child* 1999; **81:** 329–32.
3. Heger S, *et al.* Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. *J Clin Endocrinol Metab* 1999; **84:** 4583–90.
4. Carel J-C, *et al.* Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. *J Clin Endocrinol Metab* 1999; **84:** 1973–8.
5. Mul D, *et al.* Effect of gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty: final height results. *Horm Res* 2002; **58:** 1–7.
6. Carel JC, *et al.* Triptorelin 3-month CPP Study Group. Three-month sustained-release triptorelin (11.25 mg) in the treatment of central precocious puberty. *Eur J Endocrinol* 2006; **154:** 119–24.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1.

Local reactions. For reference to local reactions occurring following injection of gonadorelin analogues, including triptorelin, see Leuprorelin Acetate, p. 2286.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies triptorelin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1] For the use of triptorelin in the prevention of premenstrual exacerbations of acute porphyria, see above.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Sepsis. A report of 2 patients in whom triptorelin therapy led to sepsis caused by expulsion of necrotic fibroids through the cervix.[1]

1. Ellenbogen A, *et al.* Complication of triptorelin treatment for uterine myomas. *Lancet* 1989; **ii:** 167–8.

Interactions

As for Gonadorelin, p. 2282.2.

Pharmacokinetics

Triptorelin is rapidly absorbed after subcutaneous injection and peak plasma concentrations occur about 40 minutes after a dose. The biological half-life is about 7.5 hours, although longer half-lives have been reported in patients with prostate cancer, and shorter half-lives in some groups of healthy subjects.

References.

1. Müller FO, *et al.* Pharmacokinetics of triptorelin after intravenous bolus administration in healthy males and in males with renal or hepatic insufficiency. *Br J Clin Pharmacol* 1997; **44:** 335–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Decapeptyl; Gonapeptyl; ***Austral.***: Diphereline; ***Austria***: Decapeptyl; Pamorelin; ***Belg.***: Decapeptyl; Gonapeptyl; Salvacyl; ***Braz.***: Gonapeptyl; Neo Decapeptyl; ***Canad.***: Trelstar; ***Chile***: Decapeptyl; ***China***: Decapeptyl (达必佳); Diphereline (达菲林); ***Cz.***: Decapeptyl; Diphereline;

Denm.: Decapeptyl; Gonapeptyl; Pamorelin; Salvacyl; ***Fin.***: Decapeptyl; Gonapeptyl; Pamorelin; Salvacyl; ***Fr.***: Decapeptyl; Gonapeptyl; Salvacyl; ***Ger.***: Decapeptyl; Pamorelin; Salvacyl; ***Gr.***: Arvekap; Gonapeptyl; ***Hong Kong***: Decapeptyl; Diphereline; ***Hung.***: Decapeptyl; Diphereline; ***India***: Decapeptyl; ***Irl.***: Decapeptyl; Gonapeptyl; ***Israel***: Decapeptyl; Diphereline; ***Ital.***: Decapeptyl; Gonapeptyl; ***Malaysia***: Decapeptyl; ***Mex.***: Pamorelin; ***Neth.***: Decapeptyl; Gonapeptyl; Pamorelin; Salvacyl; Triptofem; ***Norw.***: Pamorelin; Salvapar; ***Philipp.***: Decapeptyl; ***Pol.***: Decapeptyl; Diphereline; ***Port.***: Decapeptyl; Fertipeptil; Gonapeptyl; ***Rus.***: Decapeptyl (Декапептил); Diphereline (Диферелин); ***S.Afr.***: Decapeptyl†; Gonapeptyl; ***Singapore***: Decapeptyl; ***Spain***: Decapeptyl; Gonapeptyl; ***Swed.***: Decapeptyl†; Gonapeptyl; Moapart†; Pamorelin; ***Switz.***: Decapeptyl; Pamorelin; Salvacyl; ***Thai.***: Decapeptyl; Diphereline; ***Turk.***: Decapeptyl; ***UK***: Decapeptyl; Gonapeptyl; Salvacyl; ***Ukr.***: Decapeptyl (Декапептил); Diphereline (Диферелин); ***USA***: Trelstar; ***Venez.***: Decapeptyl.

Ulipristal Acetate *(BANM, USAN, rINNM)*

Acetato de ulipristal; CDB-2914; RTI-3021-012; Uliprisnil Acetate; Ulipristal, Acétate d'; Ulipristali Acetas; VA-2914; Улипристала Ацетат.

(11β)-17-(Acetyloxy)-11-[4-(dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione.

$C_{30}H_{37}NO_4$=475.6

CAS — 159811-51-5 (ulipristal); 126784-99-4 (ulipristal acetate).

ATC — G03AD02.

ATC Vet — QG03AD02.

UNII — YF7V70N028.

Uses and Administration

Ulipristal is a progesterone receptor modulator with antagonist and partial agonist effects. It inhibits or delays ovulation, alters the endometrial epithelium, and can reduce fibroid size.

A single oral dose of ulipristal acetate 30 mg may be given for emergency contraception (p. 2233.2). It should be taken as soon as possible, and no later than 120 hours (5 days), after unprotected sexual intercourse. If vomiting occurs within 3 hours, another dose should be taken. Ulipristal is also under investigation as a continuous form of contraception.

Ulipristal acetate may be used for pre-operative management in women with symptoms of uterine fibroids (p. 2281.2). An oral dose of 5 mg once daily is used, usually for up to 3 months before surgery. Treatment should be started during the first week of a menstrual cycle. A significant reduction in menstrual blood loss or amenorrhoea is expected within the first 10 days of treatment; menstrual periods generally return within 4 weeks after stopping treatment.

References.

1. Anonymous. Ulipristal - a new emergency contraceptive pill. *Drug Ther Bull* 2010; **48**: 86–8.
2. McKeage K, Croxtall JD. Ulipristal acetate: a review of its use in emergency contraception. *Drugs* 2011; **71**: 935–45.
3. Snow SE, *et al.* Ulipristal acetate for emergency contraception. *Ann Pharmacother* 2011; **45**: 780–6.
4. Donnez J, *et al.* PEARL I Study Group. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med* 2012; **366**: 409–20.
5. Donnez J, *et al.* PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med* 2012; **366**: 421–32.

Adverse Effects and Precautions

Adverse effects reported for ulipristal acetate include abdominal pain and gastrointestinal disturbances, such as nausea and vomiting. Other effects include headache, dizziness, mood disorders, breast tenderness, myalgia, back pain, and fatigue. Less commonly reported effects have included blurred vision, vertigo, and skin reactions such as acne, rash, pruritus, and urticaria. Other adverse effects reported with continuous use include hot flushes, functional ovarian cysts that usually disappear spontaneously within a few weeks, and a few cases of uterine haemorrhage in women at risk of excessive bleeding associated with uterine fibroids. Increases in blood cholesterol and triglycerides have also been recorded.

Dysmenorrhoea is common after a dose of ulipristal acetate for emergency contraception. Menstrual disturbances can also occur and the next menstrual period may start several days earlier or later than expected after a single dose. Endometrial changes and thickening may occur in patients being treated for uterine fibroids. However, these changes are different from endometrial hyperplasia and reversible after stopping treatment. Endometrial thickening that persists 3 months after ulipristal is stopped and menstruation has returned should be investigated.

Pregnancy should be excluded before the use of ulipristal acetate for emergency contraception. In women being treated for fibroids, ulipristal acetate should be started in the first week of a menstrual cycle. Although continuous treatment causes anovulation in most patients, a non-hormonal method of contraception is recommended.

The elimination of ulipristal acetate is expected to be reduced in patients with hepatic impairment and its use in moderate or severe impairment is not recommended without close monitoring. Ulipristal acetate has a high affinity for glucocorticoid receptors, and antiglucocorticoid effects have been seen in *animal* studies. The use of ulipristal acetate is not recommended in patients who have asthma that is inadequately controlled by oral corticosteroid therapy.

Interactions

Drugs that increase gastric pH (such as antacids, H_2-receptor antagonists, and proton pump inhibitors) may reduce the absorption of ulipristal acetate. This may reduce its efficacy for emergency contraception and concomitant use is therefore not recommended. However, during continuous use the systemic exposure to ulipristal increases (with a delayed and decreased peak plasma concentration) and the effect is not expected to be clinically significant for patients being treated for uterine fibroids. Drugs that alter the activity of the cytochrome P450 isoenzyme CYP3A4 have the potential to affect the plasma concentrations of ulipristal acetate. CYP3A4 inducers may decrease its efficacy as an emergency contraceptive, and an interaction should be considered possible for at least 2 to 3 weeks after such inducers have been stopped. Concomitant use with potent inducers is not recommended with ulipristal acetate given continuously for fibroid treatment. Moderate and potent inhibitors of CYP3A4 are also not recommended with continuous therapy.

Ulipristal acetate may interfere with the action of progestogens, such as those found in combined and progestogen-only hormonal contraceptives. Regular hormonal contraception may be continued when ulipristal acetate is used for emergency contraception, but a reliable barrier method of contraception should also be used until the next menstrual period starts. The concomitant use of ulipristal acetate and levonorgestrel for emergency contraception is not recommended. A non-hormonal contraceptive method is recommended during continuous ulipristal acetate treatment of fibroids.

In-vitro studies suggest that ulipristal acetate may be an inhibitor of P-glycoprotein. Co-administration of ulipristal with substrates of this transporter protein is therefore not recommended, although clinical evidence of an interaction is lacking.

Pharmacokinetics

Ulipristal acetate is rapidly absorbed from the gastrointestinal tract; its absorption is pH-dependent and may be reduced when gastric pH is raised. The drug is highly bound to plasma proteins. It is extensively metabolised to demethylated and hydroxylated metabolites, mainly by the cytochrome P450 isoenzyme CYP3A4 and to a small extent by CYP1A2 and CYP2D6. The terminal plasma half-life of ulipristal acetate is about 32 to 38 hours after a single dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: ellaOne; ***Belg.***: ellaOne; ***Cz.***: ellaOne; ***Denm.***: ellaOne; Esmya; ***Fr.***: ellaOne; Esmya; ***Ger.***: ellaOne; ***Gr.***: ellaOne; ***Hung.***: ellaOne; ***Irl.***: ellaOne; ***Israel***: ella; ***Ital.***: ellaOne; ***Neth.***: ellaOne; Esmya; ***Norw.***: ellaOne; Esmya; ***Pol.***: ellaOne; ***Port.***: ellaOne; ***Singapore***: ella; ***Spain***: ellaOne; ***Swed.***: ellaOne; ***UK***: ellaOne; Esmya; ***Ukr.***: Dvella (Двелла); ***USA***: ella.

Urofollitropin *(BAN, USAN, rINN)*

Urofolitropin; Urofolitropin; Urofolitropina; Urofolitropinas; Urofollitrophin; Urofollitropiini; Urofollitropine; Urofollitropinum; Урофоллитропин.

CAS — 97048-13-0.

ATC — G03GA04.

ATC Vet — QG03GA04.

UNII — W9BB98U6HP.

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

Ph. Eur. 8: (Urofollitropin). A dry preparation containing menopausal gonadotrophin obtained from the urine of postmenopausal women. It has follicle-stimulating activity and no or virtually no luteinising activity. The potency is not less than 90 units of follicle-stimulating hormone per mg; the ratio of units of luteinising hormone to units of follicle-stimulating hormone is not more than 1:60. An almost white or slightly yellow powder. Soluble in water. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Urofollitropin is a gonadotrophin, obtained from the urine of postmenopausal women, possessing follicle-stimulating hormone (FSH) activity but virtually no luteinising activity. For details of the actions of FSH, see p. 2278.2.

Urofollitropin is used similarly to human menopausal gonadotrophins (p. 2284.2) in the treatment of **female infertility** with the exception that, being without luteinising hormone activity, it can be used in patients where any increase in luteinising hormone activity is not required, as in polycystic ovarian disease. Urofollitropin is given subcutaneously or intramuscularly in a dosage adjusted according to the patient's response. Usually a dose providing 75 to 150 units of FSH daily is given initially. When an adequate response is achieved, as determined by oestrogen monitoring or ultrasonic visualisation of follicles, treatment is stopped and after 1 or 2 days a single dose of chorionic gonadotrophin 5000 to 10 000 units is given to induce ovulation. Treatment with urofollitropin should be stopped if there is no response after 4 weeks although treatment may be attempted again in future cycles. US product information has recommended that a maximum daily dose of 450 units should not be exceeded, and that courses of treatment should be no longer than 12 days.

Urofollitropin is also used with other drugs as part of IVF procedures. It is typically given in a dose providing 150 to 225 units of FSH daily, usually beginning from day 2 or 3 of the menstrual cycle. Alternatively, therapy has been begun with clomifene citrate and continued with urofollitropin, or urofollitropin may be given after suppression of gonadotrophin release with a gonadorelin analogue. Treatment is continued until an adequate response is obtained and the final injection of urofollitropin is followed 1 to 2 days later by 5000 to 10 000 units of chorionic gonadotrophin. Oocyte retrieval is performed 34 to 35 hours later.

Urofollitropin is also used with chorionic gonadotrophin to stimulate spermatogenesis in the treatment of **male infertility**, although a preparation with combined luteinising activity, such as human menopausal gonadotrophins, may be preferred. The usual dose of urofollitropin provides 150 units of FSH three times a week. Treatment with urofollitropin and chorionic gonadotrophin should be continued for at least 4 months. For a brief discussion of hypogonadism see p. 2252.3.

Infertility. For reference to the use of preparations with follicle-stimulating hormone activity in infertility, see p. 2253.1.

References to the use of urofollitropin including contradictory results as to its relative efficacy versus recombinant follicle-stimulating hormone.

1. McFaul PB, *et al.* Treatment of clomiphene citrate-resistant polycystic ovarian syndrome with pure follicle-stimulating hormone or human menopausal gonadotropin. *Fertil Steril* 1990; **53**: 792–7.
2. European Metrodin HP Study Group. Efficacy and safety of highly purified urinary follicle-stimulating hormone with human chorionic gonadotropin for treating men with isolated hypogonadotropic hypogonadism. *Fertil Steril* 1998; **70**: 256–62.
3. Crain JL, *et al.* Outcome comparison of in vitro fertilization treatment with highly purified subcutaneous follicle-stimulating hormone (Fertinex, a urofollitropin) versus intramuscular menotropins. *Am J Obstet Gynecol* 1998; **179**: 299–307.
4. Lenton E, *et al.* Induction of ovulation in women undergoing assisted reproductive techniques: recombinant human FSH (follitropin alpha) versus highly purified urinary FSH (urofollitropin HP). *Hum Reprod* 2000; **15**: 1021–7.
5. Mohamed MA, *et al.* Urinary follicle-stimulating hormone (FSH) is more effective than recombinant FSH in older women in a controlled randomized study. *Fertil Steril* 2006; **85**: 1398–1403.
6. Revelli A, *et al.* Recombinant versus highly-purified, urinary follicle-stimulating hormone (r-FSH vs. HP-uFSH) in ovulation induction: a prospective, randomized study with cost-minimization analysis. *Reprod Biol Endocrinol* 2006; **4**: 38.
7. Pacchiarotti A, *et al.* Efficacy of a combined protocol of urinary and recombinant follicle-stimulating hormone used for ovarian stimulation of patients undergoing ICSI cycle. *J Assist Reprod Genet* 2007; **24**: 400–5.
8. Baker VL, *et al.* Clinical efficacy of highly purified urinary FSH versus recombinant FSH in volunteers undergoing controlled ovarian stimulation for in vitro fertilization: a randomized, multicenter, investigator-blind trial. *Fertil Steril* 2009; **91**: 1005–11.

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p. 2284.3.

Pharmacokinetics

After multiple intramuscular or subcutaneous dosing of urofollitropin, peak plasma concentrations of follicle-stimulating hormone occur about 10 hours after a dose and the elimination half-life is about 15 or 20 hours respectively.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Follitrin; Fostimon; ***Austral.***: Metrodin†; ***Austria***: Bravelle; Fostimon; ***Belg.***: Fostimon ***Braz.***: Bravelle; Fostimon; Metrodin†; ***Canad.***: Bravelle; ***Chile***: Follitrin; ***China***: Lishenbao (丽申宝); ***Cz.***: Bravelle; Fostimon

Denm.: Bravelle; Fostimon; ***Fin.***: Fostimon; ***Fr.***: Fostimon; ***Ger.***: Bravelle; ***Gr.***: Bravelle; Metrodin; ***Hong Kong***: Bravelle; Fostimon†; ***Hung.***: Fostimon; ***India***: Endogen; Fergonad-F; Folicullin; Foligem; Foligest; Folliova; Follitec; Follokon; Fostine; Gonotrop F; LG Follimon; Materna FSH; Metrodin; Neogentin; Ovitrop; Ovufol-HP; ***Irl.***: Bravelle; Fostimon; ***Israel***: Bravelle; Fostimon; ***Ital.***: Fostimon; ***Mex.***: Fostimon; ***Neth.***: Bravelle; Fostimon; ***Norw.***: Bravelle; Fostimon; ***Pol.***: Bravelle; Fostimon; ***Port.***: Bravelle; Postimon; Metrodin†; ***Rus.***: Metrodin (Метродин); ***Spain***: Bravelle; Fostipur; ***Swed.***: Bravelle; Fostimon; ***Switz.***: Fostimon; ***Thai.***: Follimon; ***Turk.***: Follegon; Fostimon; Metrodin; ***UK***: Fostimon; ***Ukr.***: Bravelle (Бравель); Fostimon (Фостимон); ***USA***: Bravelle; Fertinex†; Metrodin†.

Pharmacopoeial Preparations
BP 2014: Urofollitropin Injection.

Zeranol *(BAN, USAN, rINN)* ⊗

MK-188; P-1496; THFES (HM); Zearalanol; Zéranol; Zeranolum; Зеранол.

(3*S*,7*R*)-3,4,5,6,7,8,9,10,11,12-Decahydro-7,14,16-trihydroxy-3-methyl-1*H*-2-benzoxacyclotetradecin-1-one.

$C_{18}H_{26}O_5$=322.4

CAS — 26538-44-3.

UNII — 76LO2L2V39.

Profile

Zeranol is a nonsteroidal oestrogen that has been used for the management of menopausal and menstrual disorders. It has also been used as a growth promotor in veterinary practice. Its anabolic properties may be subject to abuse in sport.

WHO specifies an acceptable daily intake of zeranol as a residue in foods and recommends maximum residue limits in various animal tissues.[1] However, it should be noted that, in the EU the use of zeranol in veterinary medicine is prohibited. Certain other steroidal hormones are permitted for restricted use but their use as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: thirty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 763* 1988. Also available at: http://libdoc.who.int/trs/WHO_TRS_763.pdf (accessed 30/06/08)

Stimulants and Anorectics

Hyperactivity, p. 2314
Narcoleptic syndrome, p. 2314
Obesity, p. 2315
Prader-Willi syndrome, p. 2315

This chapter includes compounds used, generally under specialist supervision, for their central stimulant or their anorectic effects. Many are sympathomimetics and are subject to extensive abuse, which has led to strict limitations on their availability.

Hyperactivity

Attention deficit hyperactivity disorder (ADHD) is a syndrome of developmentally inappropriate and socially disruptive behaviour beginning in childhood and characterised by varying degrees of hyperactivity, inattention, and impulsiveness. Children with ADHD are easily distracted and have difficulty in completing tasks. Associated features may include low frustration tolerance, mood lability, and defiance. Some children continue to have symptoms throughout adolescence and into adulthood. The terms hyperkinesis, hyperkinetic syndrome, minimal brain dysfunction, attention deficit disorder, and attention deficit disorder with hyperactivity have sometimes been used synonymously for ADHD, but patients described as having these disorders do not necessarily satisfy the diagnostic criteria for ADHD.

Both drug and behaviour therapy may be used for the management of ADHD. Drug therapy is useful for the control of symptoms but is not curative and should take into account co-existing disorders such as tics, Tourette's syndrome, and epilepsy. In the USA drug treatment for ADHD is quite common even in mild forms, and in the hands of specialists appears superior to behavioural therapy, but in the UK drugs are generally reserved for severely affected children and those who fail to respond to counselling and behaviour therapy.

The central stimulant methylphenidate or the selective noradrenaline reuptake inhibitor atomoxetine are usually the drugs of first choice; dexamfetamine is an alternative in children who do not respond to these drugs. There are multiple formulations of stimulants available to allow treatment to be individualised and to improve compliance. Other stimulants that have been used include pemoline but its use was associated with hepatotoxicity which led to its withdrawal in many countries. Modafinil is under investigation for the treatment of hyperactivity disorders. Many authorities consider that young, particularly pre-school, children should not receive stimulants, although they do appear to be of use when the disorder persists into adulthood.

The use of central stimulants has been associated with sudden death and some authorities recommend screening for cardiovascular disorders before starting treatment and to monitor heart rate and blood pressure during treatment (for further details, see Effects on the Cardiovascular System, under Dexamfetamine, p. 2319.3). Children who benefit from drug therapy may require several years of treatment. Growth is not generally affected by treatment with stimulants but monitoring during treatment is advised. If growth is noted to be significantly reduced, a planned treatment break may be considered to allow growth to catch up. Treatment should be reviewed periodically to determine whether continued therapy is necessary.

Tricyclic antidepressants such as imipramine and desipramine are also used for ADHD in both children and adults and their effect appears to be independent of their antidepressant action. However, they tend to be reserved for patients who fail to respond to, or are intolerant of, central stimulants. Tricyclic antidepressants may be useful in patients with co-existing Tourette's syndrome or in those with a family history of the disorder, as some stimulants may precipitate or exacerbate associated tics (p. 1030.1). Tricyclic antidepressants might also be preferred in patients with co-existing anxiety, depression, or enuresis, or in those with a history of drug abuse. Use with central stimulants has been studied but careful monitoring is advised (see also Interactions under Dexamfetamine, p. 2320.2). MAOIs have been used successfully but problems with dietary restriction and potential drug interactions have limited their use. SSRIs such as fluoxetine have produced beneficial results as an adjunct to central stimulants in a small number of patients with associated depression or obsessive-compulsive disorder, but their value in ADHD alone is unclear. Bupropion has shown promising results in controlled studies in children but may exacerbate tics and increase the risk of seizures in predisposed patients. Venlafaxine has been effective in open studies in a small number of adult patients.

There is some evidence that carbamazepine may be an effective alternative to central stimulants. Clonidine, an $alpha_2$ agonist, has been used successfully as monotherapy, or with stimulants in children with an inadequate response to stimulants alone. However, there have been reports of adverse cardiac events associated with such combinations; some recommend performing a cardiovascular examination and an ECG before starting treatment with clonidine. Guanfacine, another $alpha_{2A}$ agonist, has also been tried successfully, and may be better tolerated. Antipsychotics can produce severe adverse effects and are probably only warranted as adjunctive therapy to central stimulants in severe cases or when there is also extremely violent or destructive behaviour. Dopaminergics such as levodopa or pergolide have been tried with beneficial results for the treatment of restless legs syndrome and periodic limb movements in sleep associated with ADHD; some improvements in ADHD symptoms were also noted on resolution of the parasomnias.

Much controversy has surrounded the hypothesis that certain synthetic food additives including preservatives and artificial flavours and colours are aetiological agents in ADHD. Controlled studies have not proved the efficacy of dietary manipulation.

References.
1. Swanson JM, *et al.* Attention-deficit hyperactivity disorder and hyperkinetic disorder. *Lancet* 1998; **351**: 429–33.
2. Zametkin AJ, Ernst M. Problems in the management of attention-deficit-hyperactivity disorder. *N Engl J Med* 1999; **340**: 40–6.
3. Elia J, *et al.* Treatment of attention-deficit-hyperactivity disorder. *N Engl J Med* 1999; **340**: 780–8.
4. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999; **56**: 1073–86.
5. Overmeyer S, Taylor E. Annotation: principles of treatment for hyperkinetic disorder: practice approaches for the UK. *J Child Psychol Psychiatry* 1999; **40**: 1147–57.
6. Trollor JN. Attention deficit hyperactivity disorder in adults: conceptual and clinical issues. *Med J Aust* 1999; **171**: 421–5.
7. Jadad AR, *et al. Treatment of attention-deficit/hyperactivity disorder.* Rockville, MD: Agency for Healthcare Research and Quality; 1999. Available at: http://www.ahcpr.gov/clinic/epcsums/adhdsum.htm (accessed 15/04/04)
8. Spencer T, *et al.* Pharmacotherapy of attention deficit hyperactivity disorder. *Child Adolesc Psychiatr Clin North Am* 2000; **9**: 77–97.
9. Anonymous. Stimulant drugs for severe hyperactivity in childhood. *Drug Ther Bull* 2001; **39**: 52–4.
10. Maidment ID. Efficacy of stimulants in adult ADHD. *Ann Pharmacother* 2003; **37**: 1884–90.
11. Wilens TE. Drug therapy for adults with attention-deficit hyperactivity disorder. *Drugs* 2003; **63**: 2395–2411.
12. Kutcher S, *et al.* International consensus statement on attention-deficit/hyperactivity disorder (ADHD) and disruptive behaviour disorders (DBDs): clinical implications and treatment practice suggestions. *Eur Neuropsychopharmacol* 2004; **14**: 11–28.
13. MTA Cooperative Group. National Institute of Mental Health multimodal treatment study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. *Pediatrics* 2004; **113**: 754–61.
14. MTA Cooperative Group. National Institute of Mental Health multimodal treatment study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. *Pediatrics* 2004; **113**: 762–9.
15. Wilens TE, *et al.* Attention-deficit/hyperactivity disorder in adults. *JAMA* 2004; **292**: 619–23.
16. Rappley MD. Attention deficit-hyperactivity disorder. *N Engl J Med* 2005; **352**: 165–73.
17. Brown RT, *et al.* The Committee on Quality Improvement, Subcommittee on Attention-Deficit/Hyperactivity Disorder. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Abstract: *Pediatrics* 2005; **115**: 1763. Full version: http://pediatrics.aappublications.org/cgi/reprint/115/6/e749 (accessed 25/04/06)
18. Wolraich ML, *et al.* Attention-deficit/hyperactivity disorder among adolescents: a review of the diagnosis, treatment, and clinical implications. *Pediatrics* 2005; **115**: 1734–46.
19. Dopheide JA. ASHP therapeutic position statement on the appropriate use of medications in the treatment of attention-deficit/hyperactivity disorder in pediatric patients. *Am J Health-Syst Pharm* 2005; **62**: 1502–9.
20. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005; **366**: 237–48. Correction. *ibid.* 2006; **367**: 210.
21. NICE. Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents: review of Technology Appraisal 13 (Technology Appraisal 98, issued March 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA098guidance.pdf (accessed 08/08/08)
22. Wolraich ML, *et al.* Treatment of attention deficit hyperactivity disorder in children and adolescents: safety considerations. *Drug Safety* 2007; **30**: 17–26.
23. Jamdar S, Sathyamoorthy BT. Management of attention-deficit/hyperactivity disorder. *Br J Hosp Med* 2007; **68**: 360–6.
24. Nutt DJ, *et al.* British Association for Psychopharmacology. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2007; **21**: 10–41.
25. Pliszka S. AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007; **46**: 894–921.
26. Harpin VA. Medication options when treating children and adolescents with ADHD: interpreting the NICE guidance 2006. *Arch Dis Child Educ Pract Ed* 2008; **93**: 58–65.
27. National Collaborating Centre for Mental Health/NICE. Attention deficit hyperactivity disorder: the NICE guideline on diagnosis and management of ADHD in children, young people and adults (issued September 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/ADHDFullGuideline.pdf (accessed 25/06/09)
28. Chavez B, *et al.* An update on central nervous system stimulant formulations in children and adolescents with attention-deficit/hyperactivity disorder. *Ann Pharmacother* 2009; **43**: 1084–95.
29. Scottish Intercollegiate Guidelines Network. Management of attention deficit and hyperkinetic disorders in children and young people: a national clinical guideline (issued October 2009). Available at: http://www.sign.ac.uk/pdf/sign112.pdf (accessed 22/10/10)
30. May DE, Kratochvil CJ. Attention-deficit hyperactivity disorder: recent advances in paediatric pharmacotherapy. *Drugs* 2010; **70**: 15–40.

Narcoleptic syndrome

Narcolepsy is characterised by excessive daytime sleepiness and irresistible sleep attacks that last from a few minutes to hours. The narcoleptic syndrome often includes **cataplexy**, a sudden short-lived loss of muscle tone and paralysis of voluntary muscles induced by strong emotions. The severity of the attack can vary and some patients have complete collapse but there is no loss of consciousness. **Sleep paralysis** consists of transient episodes of complete paralysis while falling asleep or during waking; respiration is unaffected. Some patients also have vivid auditory or visual hallucinations while falling asleep (**hypnagogic hallucinations**) or disturbed sleep.

For the management of narcoleptic syndrome the patient is initially encouraged to take planned regular short periods of sleep during the day and to avoid stressful events that may provoke attacks. If drug treatment is required then central stimulants are the main drugs used for the sleep attacks of narcolepsy. However, most are ineffective against cataplexy. The selection, dose, and timing of these drugs need to be titrated for each patient, and drug holidays have been suggested to reduce the risk of developing tolerance. Amfetamines were the first drugs used. However, methylphenidate is often preferred to dexamfetamine as it has a rapid action and is considered to have fewer adverse effects. Alternative non-amfetamine stimulants used in the treatment of narcolepsy include mazindol, which also appears to be effective in cataplexy, and modafinil and its *R*-enantiomer, armodafinil. Selegiline has been reported to improve excessive daytime sleepiness and cataplexy. There is anecdotal or other limited evidence of efficacy in narcolepsy for many other drugs but there appears to be no evidence that they are superior to the central stimulants.

Tricyclic antidepressants are the primary treatment for cataplexy and sleep paralysis. However, a recent systematic review concluded that evidence supporting the use of antidepressants in cataplexy is scarce. Imipramine and clomipramine appear to have been widely used (some consider that clomipramine is the most effective of the tricyclics for this indication); desipramine and protriptyline have also been given. The onset of action is quicker, and the effective doses seem to be lower, than when tricyclics are used for depression, although tolerance to the effect may develop after 6 to 8 months, requiring an increase in dose. The daily dose should be titrated to provide maximal protection for the time of day when symptoms usually occur.

The use of sodium oxybate at night with stimulants during the day has been reported to improve the symptoms of patients with narcoleptic syndrome.

Patients requiring treatment for both narcolepsy and cataplexy may be given central stimulants and tricyclic antidepressants but require careful monitoring as the combination may produce serious adverse effects such as cardiac arrhythmias or hypertension; see also Interactions of Dexamfetamine, p. 2320.2.

References.
1. Aldrich MS. Narcolepsy. *N Engl J Med* 1990; **323**: 389–94.
2. Parkes JD. Daytime sleepiness. *BMJ* 1993; **306**: 772–5.
3. Eisen J, *et al.* Psychotropic drugs and sleep. *BMJ* 1993; **306**: 1331–4.
4. Wise MS. Childhood narcolepsy. *Neurology* 1998; **50** (suppl 1): S37–S42.
5. Nishino S, Mignot E. Drug treatment of patients with insomnia and excessive daytime sleepiness. *Clin Pharmacokinet* 1999; **37**: 305–30.
6. Krahn LE, *et al.* Narcolepsy: new understanding of irresistible sleep. *Mayo Clin Proc* 2001; **76**: 185–94.
7. Mitler MM, Hayduk R. Benefits and risks of pharmacotherapy for narcolepsy. *Drug Safety* 2002; **25**: 791–809.
8. Zeman A, *et al.* Narcolepsy and excessive daytime sleepiness. *BMJ* 2004; **329**: 724–8.
9. Houghton WC, *et al.* Pharmacotherapy for cataplexy. *Sleep Med Rev* 2004; **8**: 355–66.
10. Dauvilliers Y, *et al.* Narcolepsy with cataplexy. *Lancet* 2007; **369**: 499–511.

11. Roth T. Narcolepsy: treatment issues. *J Clin Psychiatry* 2007; 68 (suppl 13): 16–19.
12. Nishino S. Narcolepsy: pathophysiology and pharmacology. *J Clin Psychiatry* 2007; 68 (suppl 13): 9–15.
13. Morgenthaler TI, *et al.* Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 2007; 30: 1705–11. Also available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2276123/pdf/aasm.30.12.1705.pdf (accessed 11/05/10)
14. Vignatelli L, *et al.* Antidepressant drugs for narcolepsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 08/08/08).

Obesity

Obesity results from an imbalance between energy intake and energy expenditure and increases the risk of cardiovascular disease, diabetes mellitus, gallstones, respiratory disease, osteoarthritis, and some forms of cancer. The prevalence of obesity is increasing especially in developed countries and is a particular concern in children. Obesity may be defined in terms of the body-mass index (BMI), which is the weight (kg) divided by the square of the height (m^2):

- BMI 25.0 to 29.9: overweight
- BMI 30.0 to 34.9: obese, moderate risk of comorbidity
- BMI 35.0 to 39.9: obese, severe risk of comorbidity
- BMI 40.0 or more: obese, very severe risk of comorbidity

Weight loss appears to improve control of diabetes mellitus and hypertension, and to reduce cardiovascular risk factors but long-term benefits are difficult to assess as weight is often regained.

Initial management involves dietary modification and includes calorie restriction and changes in the dietary proportions of fat, protein, and carbohydrates. Physical activity should also be increased and excess alcohol avoided. These measures should be followed for at least 3 months. If there has then been less than 10% reduction in weight and the BMI is still above 30, drug treatment may be considered. For patients with associated risk factors such as diabetes mellitus, ischaemic heart disease, hyperlipidaemias, hypertension, or sleep apnoea, drugs may be considered when the BMI is 27 or 28. Combination drug therapy is not recommended. Drugs should be given initially for 12 weeks. If weight loss is less than 5% then they should be considered a failure and stopped. If weight loss is more than 5% they may be continued and the patient monitored at monthly intervals. Treatment should be stopped once the BMI falls below 30 (or 27/28 as appropriate, see above), or if weight is regained, or there is any suspicion of toxicity. Drug treatment should only be considered for obese children after lifestyle interventions have been initiated, and who have associated conditions such as orthopaedic problems or sleep apnoea.

Many drugs are capable of reducing appetite and have been used as such in the treatment of obesity. Both centrally acting (appetite suppressant, anorectic) drugs and those with a local action on the gastrointestinal tract have been used. However, toxicity has been a major problem with centrally acting drugs and very few are still in current use.

Appetite suppressants can be divided into two main groups: central stimulants that act on central catecholamine pathways and drugs acting on central serotonin pathways. Stimulants such as the amfetamines and phenmetrazine are no longer recommended because of their addictive potential. Other stimulants that have been used include diethylpropion, phentermine, mazindol, and phenylpropanolamine but they are also no longer recommended. The serotonergic drugs dexfenfluramine and fenfluramine were formerly used in long-term therapy (up to 1 year) but have both been associated with valvular heart defects and have generally been withdrawn worldwide. There have also been reports of valvular heart defects in patients receiving combinations of anorectics. Rimonabant, a cannabinoid type-1 receptor antagonist, has been used as an adjunct in the treatment of obesity but was withdrawn from most markets after concern about psychiatric reactions. Guidelines have recommended the centrally acting serotonin and noradrenaline reuptake inhibitor sibutramine, and the gastric lipase inhibitor orlistat, as appropriate choices for the drug treatment of obesity, along with diet and exercise. A systematic review of long-term studies (1 year or more) found orlistat and sibutramine to be modestly effective in reducing weight. However, the marketing authorisation for sibutramine was suspended in the EU and withdrawn in the USA after a safety review found that the cardiovascular risks outweighed the benefits (for further details see Effects on the Cardiovascular System, under Sibutramine Hydrochloride, p. 2330.2). It remained available in some other countries. The selective serotonin 5-HT_{2C} agonist lorcaserin is now licensed for the management of obesity.

Many other drugs have been tried, including fluoxetine, which has met with some success, and ephedrine with caffeine. The antiepileptics topiramate and zonisamide have also been investigated and topiramate is available as a modified-release combination preparation with phentermine for the management of obesity. The biguanide antidiabetic metformin, liraglutide, an analogue of the incretin hormone, glucagon-like peptide 1 (GLP-1), and the serotonin, noradrenaline and dopamine re-uptake inhibitor tesofensine are other areas of interest. Bulk-forming drugs such as methylcellulose and sterculia have been used in an attempt to control appetite by the local effect they might exert when they swell in the gastrointestinal tract, but there is little evidence of efficacy. Nondigestible fat substitutes such as sucrose polyesters have been promoted by the food industry, as part of a strategy to reduce fat and calories in the diet to aid body-weight control.

Bariatric surgery may be considered in severely obese patients including children with comorbidities when other measures have failed.

The control of appetite and the mechanisms of obesity are under investigation. A gene, called the ob-gene, and its protein product, leptin, have been identified and appear to be involved in regulation of food intake.

References.
1. Kolanowski J. A risk-benefit assessment of anti-obesity drugs. *Drug Safety* 1999; 20: 119–31.
2. Collazo-Clavell ML. Safe and effective management of the obese patient. *Mayo Clin Proc* 1999; 74: 1235–60.
3. Egger G, *et al.* The effectiveness of popular, non-prescription weight loss supplements. *Med J Aust* 1999; 171: 604–8.
4. WHO. Obesity: preventing and managing the global epidemic. *WHO Tech Rep Ser 894* 2000. Available at: http://libdoc.who.int/trs/WHO_TRS_894.pdf (accessed 11/08/08)
5. Glazer G. Long-term pharmacotherapy of obesity 2000: a review of efficacy and safety. *Arch Intern Med* 2001; 161: 1814–24.
6. Yanovski SZ, Yanovski JA. Obesity. *N Engl J Med* 2002; 346: 591–602.
7. Hitchcock Noël P, Pugh JA. Management of overweight and obese adults. *BMJ* 2002; 325: 757–61.
8. Fernández-López JA, *et al.* Pharmacological approaches for the treatment of obesity. *Drugs* 2002; 62: 915–44.
9. Royal College of Physicians of London. *Anti-obesity drugs: guidance on appropriate prescribing and management.* Salisbury: Royal College of Physicians of London, 2003.
10. McTigue KM, *et al.* Screening and interventions for obesity in adults: summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2003; 139: 933–49.
11. Kopelman PG, Grace C. New thoughts on managing obesity. *Gut* 2004; 53: 1044–53.
12. Snow V, *et al.* Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2005; 142: 525–31.
13. Li Z, *et al.* Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005; 142: 532–46.
14. Ioannides-Demos LL, *et al.* Pharmacotherapy for obesity. *Drugs* 2005; 65: 1391–1418.
15. Haslam DW, James WPT. Obesity. *Lancet* 2005; 366: 1197–1209.
16. Wadden TA, *et al.* Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med* 2005; 353: 2111–20.
17. Daniels SR, *et al.* Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. *Circulation* 2005; 111: 1999–2012.
18. Speiser PW, *et al.* Obesity Consensus Working Group. Childhood obesity. *J Clin Endocrinol Metab* 2005; 90: 1871–87.
19. National Collaborating Centre for Primary Care/NICE. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children (issued December 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG43NICEGuideline.pdf (accessed 11/02/10)
20. Thompson WG, *et al.* Treatment of obesity. *Mayo Clin Proc* 2007; 82: 93–101.
21. Freemark M. Pharmacotherapy of childhood obesity: an evidence-based, conceptual approach. *Diabetes Care* 2007; 30: 395–402.
22. Rucker D, *et al.* Long term pharmacotherapy for obesity and overweight: updated meta-analysis. Abridged version: *BMJ* 2007; 335: 1194–9. Full version: http://www.bmj.com/cgi/reprint/335/7631/1194 (accessed 21/05/08)
23. Barlow SE. Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007; 120 (suppl 4): S164–S192.
24. August GP, *et al.* Endocrine Society. Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion. *J Clin Endocrinol Metab* 2008; 93: 4576–99.
25. Bray GA, Wilson JF. In the clinic: obesity. *Ann Intern Med* 2008; 149: ITC4–1–ITC4–15. Correction. *ibid.* 2009; 150: 363. Also available at: http://www.annals.org/content/149/7/ITC4-1.full.pdf (accessed 05/02/10)
26. Oude Luttikhuis H, *et al.* Interventions for treating obesity in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 11/02/10).
27. Scottish Intercollegiate Guidelines Network. Management of obesity (issued February 2010). Available at: http://www.sign.ac.uk/pdf/sign115.pdf (accessed 05/05/10)

Prader-Willi syndrome

Compulsive eating and a voracious appetite are two of the many clinical features of Prader-Willi syndrome, a congenital disorder characterised by infantile hypotonia, hypogonadism, and facial dysmorphism, with subsequent development of abnormalities of behaviour and intellect.[1-3] Supervision and restricted access to food are the mainstay in preventing obesity, but are commonly not sufficient. Fluoxetine may decrease food intake in some patients. It has also been tried for associated self-mutilatory behaviour (skin picking) with variable results.[4,5] Growth hormone may be of benefit in increasing associated short stature and decreasing percentage body fat,[6-12] but close surveillance of glucose homoeostasis is advisable and there have been reports of fatalities in patients with severe obesity or risk factors for respiratory impairment or obstruction.[13] Anorectics have been ineffective.[2]

1. Donaldson MDC, *et al.* The Prader-Willi syndrome. *Arch Dis Child* 1994; 70: 58–63.
2. Couper RTL, Couper JJ. Prader-Willi syndrome. *Lancet* 2000; 356: 673–5.
3. Goldstone AP, *et al.* Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab* 2008; 93: 4183–97.
4. Warnock JK, Kestenbaum T. Pharmacologic treatment of severe skin-picking behaviors in Prader-Willi syndrome. *Arch Dermatol* 1992; 128: 1623–5.
5. Schepis C, *et al.* Failure of fluoxetine to modify the skin-picking behaviour of Prader-Willi syndrome. *Australas J Dermatol* 1998; 39: 57–60.
6. Lindgren AC, *et al.* Five years of growth hormone treatment in children with Prader-Willi syndrome. *Acta Paediatr Suppl* 1999; 433: 109–11.
7. Myers SE, *et al.* Physical effects of growth hormone treatment in children with Prader-Willi syndrome. *Acta Paediatr Suppl* 1999; 433: 112–14.
8. Burman P, *et al.* Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev* 2001; 22: 787–99.
9. Paterson WF, Donaldson MDC. Growth hormone therapy in the Prader-Willi syndrome. *Arch Dis Child* 2003; 88: 283–5.
10. Elholzer U, *et al.* Growth hormone and body composition in children younger than 2 years with Prader-Willi syndrome. *J Pediatr* 2004; 144: 753–8.
11. Carrel AL, *et al.* Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr* 2004; 145: 744–9.
12. Mogul HR, *et al.* Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial. *J Clin Endocrinol Metab* 2008; 93: 1238–45.
13. Staffer F, Wallis C. Prader-Willi syndrome: who can have growth hormone? *Arch Dis Child* 2008; 93: 341–5.

Adrafinil (rINN) ⊗

Adrafinilo; Adrafinilum; CRL-40028; Адрафинил.
2-[(Diphenylmethyl)sulfinyl]acetohydroxamic acid.
$C_{15}H_{15}NO_3S$=289.3
CAS — 63547-13-7.
ATC — N06BX17.
ATC Vet — QN06BX17.
UNII — BI81Z4542G.

Profile

Adrafinil is a central stimulant and alpha$_1$-adrenergic agonist chemically related to modafinil (p. 2327.2). It is given orally for mental function impairment in the elderly in doses of 600 mg to 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Olmifon†.

Almitrine Dimesilate (BANM, rINNM)

Almitrina, dimesilato de; Almitrine Bismesylate; Almitrine, Dimésilate d'; Almitrine Dimesylate; Almitrine Mesylate (USAN); Almitrini Dimesilas; Dimesilato de almitrina; S-2620 (almitrine or almitrine dimesilate); Альмитрина Димезилат.
N,N'-Diallyl-6-[4-(4,4'-difluorobenzhydryl)piperazin-1-yl]-1,3,5-triazine-2,4-diyldiamine bis(methanesulphonate).
$C_{36}H_{29}F_2N_7,2CH_4SO_3$=669.8
CAS — 27469-53-0 (almitrine); 29608-49-9 (almitrine dimesilate).
ATC — R07AB07.
ATC Vet — QR07AB07.
UNII — 6RY6V6XM8T.

Pharmacopoeias. In *Chin.*

Profile

Almitrine dimesilate has been used as a respiratory stimulant in acute respiratory failure associated with conditions such as chronic obstructive pulmonary disease (see Respiratory System Disorders, below). Usual oral doses range from 50 to 100 mg daily and treatment may be intermittent. Up to 3 mg/kg has been given daily by intravenous infusion in 2 or 3 divided doses, each dose being infused over 2 hours. It is also available in a compound preparation with raubasine for mental function impairment in the elderly.

Mental impairment. References.

1. Poitrenaud J, *et al.* Almitrine-raubasine and cognitive impairment in the elderly: results of a 6-month controlled multicenter study. *Clin Neuropharmacol* 1990; 13 (suppl 3): S100–S108.
2. Poitrenaud J, *et al.* Time course of age-associated memory impairment in 8037 patients treated with Duxil for 6 months. *Rev Geriatr* 1994; 19: 531–8.
3. Poitrenaud J, *et al.* Memory disorders in 8037 elderly patients with age-associated memory impairment: multicenter trial with a 6-month follow-up under almitrine-raubasine. *Eur Neurol* 1995; 35 (suppl 1): 43–6.
4. Allain H, Bentue-Ferrer D. Clinical efficacy of almitrine-raubasine: an overview. *Eur Neurol* 1998; 39 (suppl 1): 39–44.

Respiratory system disorders. Respiratory stimulants (such as almitrine) have a limited and short-term role in acute respiratory failure in chronic obstructive pulmonary disease (p. 1199.1). Almitrine has been reported[1-4] to

improve ventilation and blood oxygenation, and to decrease the number of episodes of dyspnoea and hospital admissions, although others[5] have failed to note benefit. There are also reports[6,7] of beneficial effects when used with inhaled nitric oxide in patients with severe hypoxaemic acute respiratory distress syndrome (p. 1599.3) as well as in patients with hypoxia caused by focal lung lesions.[8] However, any modest benefits may be outweighed by the adverse effects, which have included peripheral paraesthesia and weight loss,[1] and headache, urticaria, breathlessness, diarrhoea, chest pain, nausea, and vomiting.[3] The peripheral neuropathy that sometimes occurs during long-term use of almitrine[9,10] may be due to an underlying feature of the pulmonary disease being treated,[11-13] although some disagree with this.[14]

1. Watanabe S, *et al.* Long-term effect of almitrine bismesylate in patients with hypoxemic chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: 1269–73.
2. Daskalopoulou E, *et al.* Comparison of almitrine bismesylate and medroxyprogesterone acetate on oxygenation during wakefulness and sleep in patients with chronic obstructive lung disease. *Thorax* 1990; 45: 666–9.
3. Bakran I, *et al.* Double-blind placebo controlled clinical trial of almitrine bismesylate in patients with chronic respiratory insufficiency. *Eur J Clin Pharmacol* 1990; 38: 249–53.
4. Górecka D, *et al.* Effects of almitrine bismesylate on arterial blood gases in patients with chronic obstructive pulmonary disease and moderate hypoxaemia: a multicentre, randomised, double-blind, placebo-controlled study. *Respiration* 2003; 70: 275–83.
5. Sans-Torres J, *et al.* Long-term effects of almitrine bismesylate in COPD patients with chronic hypoxaemia. *Respir Med* 2003; 97: 599–605. Correction. *ibid.*: 1243.
6. Jolliet P, *et al.* Additive beneficial effects of the prone position, nitric oxide, and almitrine bismesylate on gas exchange and oxygen transport in acute respiratory distress syndrome. *Crit Care Med* 1997; 25: 786–94.
7. Gallart L, *et al.* The NO Almitrine Study Group. Intravenous almitrine combined with inhaled nitric oxide for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; 158: 1770–7.
8. Payen D, *et al.* Inhaled nitric oxide, almitrine infusion, or their coadministration as a treatment of severe hypoxemic focal lung lesions. *Anesthesiology* 1998; 89: 1157–65.
9. Chedru F, *et al.* Peripheral neuropathy during treatment with almitrine. *BMJ* 1985; 290: 896.
10. Gherardi R, *et al.* Peripheral neuropathy in patients treated with almitrine dimesylate. *Lancet* 1985; i: 1247–50.
11. Suggett AJ, *et al.* Almitrine and peripheral neuropathy. *Lancet* 1985; ii: 830–1.
12. Alani SM, *et al.* Almitrine and peripheral neuropathy. *Lancet* 1985; ii: 1251.
13. Moore N, *et al.* Peripheral neuropathy in chronic obstructive lung disease. *Lancet* 1985; ii: 1311.
14. Louarn F, Gherardi R. Almitrine and peripheral neuropathy. *Lancet* 1985; ii: 1068.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Vectarion; *Fr.*: Vectarion†; *Irl.*: Vectarion†; *Pol.*: Armanor†; *Port.*: Vectarion†; *Rus.*: Armanor (Арманор); *Spain*: Vectarion†.

Multi-ingredient Preparations. *China*: Duxil (都可喜); *Hong Kong*: Duxaril; *Philipp.*: Duxaril; *Singapore*: Duxaril; *Thai.*: Duxaril†.

Amfetamine *(BAN, rINN)* ⊗

Amfetamiini; Amfetamin; Amfétamine; Amfetaminum; Amphetamine; Amphetaminum; Anfetamina; Racemic Desoxynorephedrine; Амфетамин.

(*R,S*)-α-Methylphenethylamine.

$C_9H_{13}N$=135.2

CAS — 300-62-9 (amfetamine); 139-10-6 (amfetamine phosphate).

ATC — N06BA01.

ATC Vet — QN06BA01.

UNII — CK833KGX7E.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of amfetamine:

A; Affe; Aimies; Amf; Amfa; Amfis; Amp; Amph; Amphes; Amphet; Anfes; Anfetas; A-Plus; Back dex; Bam; Bambinos; Bass; B-bombs; Beans; Bennie; Bennies; Benny and the Jets; Bens; Benz; Benzedrine; Benzidrine; Berick; Billy; Billy Whizz; Biphetamine; Bippies; Black beauties; Black birds; Black bombers; Black cadillacs; Black hollies; Black mollies; Black and white; Blacks; Blue belly; Blue boy; Blue mollies; Bolt; Bombido; Bombita; Bombitas; Boostant; Bottles; Brain pills; Brain ticklers; Brownies; Browns; Bumblebees; Candy; Cartwheels; Chalk; Chicken powder; Chocolate; Christina; Christmas tree; Clear rocks; Coast to coast; Coasts to coasts; Colorado Rockies; Co-pilot; Crank; Crisscross; Croke; Cross tops; Cross-tops; Crossroads; Crystal; Crystal methadrine; Debs; Dex; Dexadrine; Dexedrine; Dexies; Diamonds; Diet Coke; Diet pills; Dolls; Dominoes; Double cross; Drivers; Eve; Eye opener; Eye openers; Fast; Fast balls; Fastin; Fives; Fly Boys; Football; Footballs; Forwards; French blue; French blues; Gaggler; Gas; GB's; Glass; Go; Go-ee; Goey; Greenies; Halloo-Wach; Hanyak; Head drugs; Head fruit; Hearts; Hi speeds; High speed; Höökipulveri; Horse heads; Hydro; Iboga; Ice; Inbetweens; Jam; Jam cecil; Jelly baby; Jelly bean; Jelly beans; Johnny go fast; Jolly bean; Jolly beans; Jugs; Khat; L. A.; La Glass; LA ice; LA turnarounds; Leapers; Lid poppers; Lid proppers; Lightning; Lip poppers; Little bomb; Little Guys; Louee; Louie; Macka; 357 Magnum; 357 Magnums; MAO; Marathons; Marching Powder; Meth; Methedrine; Methlies Quik; Mini beans; Mini berries; Minibennie; Mollies; Monoamine oxidase; Morning shoot; Morning shot; Nineteen; Nitro; Nugget; Oranges; Peaches; Pep; Pep pills; Pervitiini; Pink hearts; Pixies; Pollutants; Powder; Proszek; Pulver; Purple hearts; Rhythm; Rippers; Road dope; Rosa; Roses; Shight; Shighty; Slammin'; Slamming; Slipvins; Snap; Snow; Snow pallets; Sparkle plenty; Sparklers; Speckled birds; Speckled eggs; Speed; Speed ball; Speed balls; Speed cristal; Speedball; Spivias; Splash; Splivins; Sprinkles; Star; Strawberry shortcake; Sulph; Sulphate; Sulphates; Sweeties; Sweets; Tens; The C; Thrusters; Toffee whizz; Topette; TR-6s; Truck drivers; Turkey; Turnabout; Turnarounds; Tweak; Tweek; Up; Uppers; Uppies; U.S.P.; Wake amine; Wake ups; Water; West Coast turnarounds; Wheels; Whiffle dust; Whiffledust; White; White Cross; White Crunch; Whites; Whiz; Whizz; Wire; X; X-mas tree; Zoomers.

Amfetamine Sulfate *(BANM, rINNM)* ⊗

Amfetamiinisulfaatti; Amfétamine, sulfate d'; Amfetamine Sulphate; Amfetamini Sulfas; Amfetamino sulfatas; Amfetaminsulfat; Amfetamin-sulfát; Amfetamin-szulfát; Amphetamine Sulfate; Amphetamine Sulphate; Amphetamini Sulfas; Anfetamina, sulfato de; Phenaminum; Phenylaminopropanum Racemicum Sulfuricum; Sulfato de anfetamina; Амфетамина Сульфат.

(*R,S*)-α-Methylphenethylamine sulphate.

$(C_9H_{13}N)_2,H_2SO_4$=368.5

CAS — 60-13-9.

ATC — N06BA01.

ATC Vet — QN06BA01.

UNII — 6DPV8NK46S.

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

Ph. Eur. 8: (Amfetamine Sulfate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Amphetamine Sulfate). A white odourless crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether. Its solutions are acid to litmus, having a pH of 5 to 6.

Incompatibility. Amfetamine sulfate is incompatible with alkalis and calcium salts.

Profile

Amfetamine is an indirect-acting sympathomimetic with actions and uses similar to those of its isomer dexamfetamine (p. 2319.1). Amfetamine sulfate and amfetamine aspartate are usually given as oral combination preparations also containing dexamfetamine salts. The laevo-isomer, levamfetamine was formerly used. Amfetamine, being volatile, was formerly given by inhalation; it has also been given orally.

Breast feeding. Amfetamine is concentrated in breast milk and the American Academy of Pediatrics has stated[1] that it has caused irritability and poor sleep pattern in breast-fed infants when used as a drug of abuse by mothers.

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 15/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Adderall; *USA*: Adderall; MAS-ER.

Pharmacopoeial Preparations

USP 36: Amphetamine Sulfate Tablets.

Ammonium Camphocarbonate

Canfocarbonato de amonio.

$C_{11}H_{19}NO_3$=213.3

CAS — 5972-75-8.

Profile

Ammonium camphocarbonate has been used in preparations for the treatment of respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Spain*: Pulmofasa.

Armodafinil *(USAN, rINN)* ⊗

Armodafinilo; Armodafinilum; CEP-10953; CRL-40982; Армодафинил.

2-[(*R*)-(Diphenylmethyl)sulfinyl]acetamide.

$C_{15}H_{15}NO_2S$=273.4

CAS — 112111-43-0.

UNII — V63XWA605I.

Profile

Armodafinil is the *R*-enantiomer of modafinil (p. 2327.2) and is used similarly in the treatment of excessive daytime sleepiness associated with the narcoleptic syndrome (p. 2314.3), obstructive sleep apnoea, and shift-work sleep disorder. In the treatment of the narcoleptic syndrome or obstructive sleep apnoea, armodafinil is given orally in a single dose of 150 or 250 mg in the morning. For the management of shift-work sleep disorder, the daily dose is 150 mg taken as a single dose 1 hour before starting work. Reduced doses are recommended in the elderly and in patients with severe hepatic impairment.

References.

1. Harsh JR, *et al.* The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin* 2006; 22: 761–74.
2. Roth T, *et al.* Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. *Clin Ther* 2006; 28: 689–706.
3. Hirshkowitz M, *et al.* Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. *Respir Med* 2007; 101: 616–27.
4. Czeisler CA, *et al.* Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. *Mayo Clin Proc* 2009; 84: 958–72.
5. Krystal AD, *et al.* A double-blind, placebo-controlled study of armodafinil for excessive sleepiness in patients with treated obstructive sleep apnea and comorbid depression. *J Clin Psychiatry* 2010; 71: 32–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Nuvigil.

Atomoxetine Hydrochloride

(BANM, USAN, rINNM)

Atomoxétine, Chlorhydrate d'; Atomoxetini Hydrochloridum; Hidrocloruro de tomoxetina; LY-135252; LY-139602; LY-139603; Tomoxetina, hidrocloruro de; Tomoxetine Hydrochloride; Томоксетина Гидрохлорид.

(-)-*N*-Methyl-γ-(2-methylphenoxy)-benzenepropanamine hydrochloride.

$C_{17}H_{21}NO,HCl$=291.8

CAS — 83015-26-3 (atomoxetine); 82248-59-7 (atomoxetine hydrochloride).

ATC — N06BA09.

ATC Vet — QN06BA09.

UNII — 57WVB6I2W0.

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

Ph. Eur. 8: (Atomoxetine Hydrochloride). A white or almost white powder. Sparingly soluble in water; soluble in anhydrous alcohol; practically insoluble in heptane. It shows polymorphism.

USP 36: (Atomoxetine Hydrochloride). A white to practically white solid. Sparingly soluble in water.

Uses and Administration

Atomoxetine hydrochloride is a selective noradrenaline reuptake inhibitor used in the treatment of attention deficit hyperactivity disorder (see Hyperactivity, p. 2314.1) in adults and children aged 6 years and over. It is given orally as the hydrochloride although doses are expressed in terms of the base; atomoxetine hydrochloride 11.4 mg is equivalent to about 10 mg of atomoxetine.

- In *children and adolescents weighing 70 kg and under*, the initial dose is the equivalent of about 500 micrograms/kg daily; this may be gradually increased to about 1.2 mg/kg daily. Licensed product information states that the total daily dose in this group should not exceed 1.4 mg/kg or 100 mg, whichever is less; however, the *BNFC* suggests that up to 1.8 mg/kg daily (maximum of 120 mg daily) may be given under specialist supervision
- In *adults and adolescents and children weighing over 70 kg*, the initial dose is the equivalent of 40 mg daily, gradually increased to 80 mg daily. Licensed product information permits a further increase, after 2 to 4 weeks, to a maximum of 100 mg daily; however, the *BNFC* suggests

that up to 120 mg daily may be given under specialist supervision

Doses may be given as either a single dose in the morning or as equally divided doses in the morning and late afternoon or early evening. US licensed product information recommends that an increase in dose can be made after a minimum of 3 days although, in the UK, at least 7 days of treatment is suggested before any increases.

In patients taking atomoxetine for extended periods, the need for continued treatment beyond 1 year should be assessed periodically.

Reduced doses are recommended in patients with hepatic impairment, see below. A lower initial dose and slower titration of atomoxetine may be required in patients who are poor CYP2D6 metabolisers (see Adverse Effects and Precautions, and Pharmacokinetics, below) and in those also taking CYP2D6 inhibitors (see Interactions, below). US licensed product information recommends increasing to the usual target dose only if symptoms fail to improve after 4 weeks and the initial dose is well tolerated in these patients.

References.

1. Michelson D, *et al.* Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Abstract: *Pediatrics* 2001; 108: 1197. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/5/e83 (accessed 15/04/04)
2. Simpson D, Plosker GL. Atomoxetine: a review of its use in adults with attention deficit hyperactivity disorder. *Drugs* 2004; 64: 205–22.
3. Kelsey DK, *et al.* Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial. Abstract: *Pediatrics* 2004; 114: 240. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/1/e1 (accessed 14/05/08)
4. Corman SL, *et al.* Atomoxetine: the first nonstimulant for the management of attention-deficit/hyperactivity disorder. *Am J Health-Syst Pharm* 2004; 61: 2391–9.
5. Gibson AP, *et al.* Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother* 2006; 40: 1134–41.
6. Wilens TE, *et al.* Long-term atomoxetine treatment in adolescents with attention-deficit/hyperactivity disorder. *J Pediatr* 2006; 149: 112–19.
7. Newcorn JH, *et al.* Low-dose atomoxetine for maintenance treatment of attention-deficit/hyperactivity disorder. Abstract: *Pediatrics* 2006; 118: 2527. Full version: http://pediatrics.aappublications.org/cgi/reprint/118/6/e1701 (accessed 14/05/08)
8. Bangs ME, *et al.* Atomoxetine ADHD/ODD Study Group. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder and oppositional defiant disorder. Abstract: *Pediatrics* 2008; 121: 383–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/121/2/e314 (accessed 22/01/10)

Administration in children. For doses of atomoxetine in children and adolescents, see Uses and Administration, p. 2316.3.

Administration in hepatic impairment. In patients with moderate hepatic impairment (Child-Pugh class B) the dose of atomoxetine (see Uses and Administration, p. 2316.3) should be reduced by 50%, while in those with severe impairment (Child-Pugh class C) it should be reduced by 75%.

References.

1. Chalon SA, *et al.* Effect of hepatic impairment on the pharmacokinetics of atomoxetine and its metabolites. *Clin Pharmacol Ther* 2003; 73: 178–91.

Adverse Effects and Precautions

Adverse effects of atomoxetine include dyspepsia and other gastrointestinal disturbances, anorexia and weight loss, fatigue, sleep disturbances, dizziness, cough, sinusitis or rhinorrhoea, urinary hesitancy or retention, decreased libido and sexual dysfunction, priapism, rashes, increased sweating, and hot flushes. Psychotic or manic symptoms (such as hallucinations, delusional thinking, mania, or agitation) and aggressive behaviour, hostility, or emotional lability have occurred; suicidal behaviour has also been reported (see Effects on Mental State, below). Hypersensitivity reactions have occurred rarely. There have also been rare reports of severe hepatotoxicity (see Effects on the Liver, below).

There may be increases in blood pressure and heart rate, and atomoxetine should be given with caution to patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease (see also Effects on the Cardiovascular System, under Dexamfetamine Sulfate, p. 2319.3). Orthostatic hypotension and syncope have also been reported. QT prolongation has been associated with atomoxetine therapy and it should be used with caution in patients with known or suspected prolonged QT interval. Use with drugs liable to inhibit the cytochrome P450 isoenzyme CYP2D6, other drugs that may prolong the QT interval, or drugs likely to cause electrolyte imbalance may also increase the risk (see Interactions, below). Sudden death, stroke, and myocardial infarction have also been reported in patients given atomoxetine. All patients should be assessed for cardiovascular disease before treatment is started. Atomoxetine should generally not be used in those with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems.

Seizures are a potential risk with atomoxetine therapy and it should be used with caution in patients with a history of seizures; treatment may need to be stopped in those who develop seizures or have an increase in seizure frequency.

Atomoxetine is contra-indicated in patients with angle-closure glaucoma as it may increase the risk of mydriasis.

The weight and height gain of children receiving atomoxetine has been reported to lag behind that of the predicted norm for about the first 9 to 12 months of treatment and generally normalises within about the first 3 years of treatment; licensed product information recommends that growth be monitored and consideration given to dose reduction or interrupting treatment in patients who are not growing or gaining weight satisfactorily.

Poor metabolisers of atomoxetine (see Pharmacokinetics, below) may have an increased risk of adverse reactions.

Effects on the liver. In December 2004, the US manufacturer stated that 2 cases of severe hepatotoxicity had been reported with atomoxetine treatment since the drug was launched in 2002.[1] In both cases the patients recovered; however, because of the risk of acute hepatic failure resulting in death or the need for transplantation, it was recommended that atomoxetine should be permanently discontinued in patients with jaundice or markedly increased liver enzyme values.

Similar advice was also issued in the UK by the CSM.[2] Up to February 2005, the CSM were aware of 3 reports of hepatic disorders (one each of hepatitis, jaundice, and increased bilirubin) with atomoxetine treatment in the UK; a total of 41 reports of hepatic disorders had been received worldwide.

A further report by the US manufacturer covered clinical study data in 7961 patients as well as 4 years postmarketing experience (since 2002) in about 4.3 million patients. Of the 7961 patients who received atomoxetine in studies, 41 had hepatobiliary events; most were mild increases in ALT and AST levels. None progressed to liver failure. Postmarketing experience indicated that there were only 3 spontaneously reported cases of reversible drug-induced liver injury probably related to atomoxetine use.[3]

1. Eisenberg P. Lilly. Safety data on Strattera (atomoxetine hydrochloride)–hepatic effects (issued 21st December, 2004).
2. MHRA. Strattera (atomoxetine)–risk of hepatic disorders. Message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 2nd February 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019459&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
3. Bangs ME, *et al.* Hepatic events associated with atomoxetine treatment for attention-deficit hyperactivity disorder. *Drug Safety* 2008; 31: 345–54.

Effects on mental state. In an observational study of 153 children, irritability, aggression, mania, or hypomania were associated with atomoxetine in 51 cases. Of these, 31 had a family history, and 41 a personal history, of mood disorders; 27 had both and 6 had neither. The authors therefore recommended that all patients receiving atomoxetine should be monitored closely.[1]

Subsequently, the FDA[2] requested the US manufacturer (*Eli Lilly*) to conduct an analysis of adverse events from 12 clinical studies involving 2208 patients. The risk of suicidal behaviour during the first few months of treatment was found to be 0.4% in children receiving atomoxetine compared with no risk in those on placebo; no suicides were reported although there was one unsuccessful suicide attempt in the atomoxetine-treated group. This finding resulted in the inclusion of a warning in US labelling about the increased risk of suicidal ideation in children and adolescents being treated with atomoxetine; it was also recommended that changes in behaviour must be closely monitored, particularly during the initial months of therapy or when the dose is changed. Similar warnings were issued by the UK CSM[3] and regulatory authorities in other countries.[4]

In light of these concerns a review of available data in Europe was conducted in 2006; it was considered that the overall risk to benefit ratio of atomoxetine in children remained favourable.[5]

An update published by Health Canada[6] noted 189 reports of adverse reactions associated with atomoxetine by December 2007; of these, 55 were reported as suicide attempts of which one was successful. A reminder to monitor moods, behaviours, thoughts, and feelings during treatment was given.

1. Henderson TA, Hartman K. Aggression, mania, and hypomania induction associated with atomoxetine. *Pediatrics* 2004; 114: 895–6.
2. FDA. FDA alert for healthcare professionals: atomoxetine (marketed as Strattera)–suicidal thinking in children and adolescents (issued 29th September, 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124391.htm (accessed 22/01/10)
3. MHRA. Strattera (atomoxetine): risk of suicidal thoughts/behaviour. Message from Professor G Duff, Chairman of Committee on Safety of Medicine (issued 29th September, 2005). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2018039.pdf (accessed 11/08/08)
4. Lilly, Canada. WARNING for atomoxetine regarding the potential for behavioural and emotional changes, including risk of self-harm (issued 28th September, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/strattera_hpc-cps-eng.pdf (accessed 08/08/08)
5. MHRA. Updated warnings on the attention deficit hyperactivity disorder drug Strattera: information for healthcare professionals. Message from Professor G Duff, Chairman of Commission on Human Medicines (issued 16th February, 2006). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2018039.pdf (accessed 22/01/10)
6. Health Canada. Atomoxetine and suicidal behaviour: update. *Can Adverse React News* 2008; 18 (3): 2–3. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v18n3-eng.php (accessed 22/01/10)

Handling. Atomoxetine is an ocular irritant and atomoxetine capsules should not therefore be opened. If the capsule contents do accidentally come into contact with the eye, the affected eye must be flushed immediately with water; hands and other potentially contaminated surfaces should be washed as soon as possible.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atomoxetine 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 25/10/11)

Tourette's syndrome. There is, at best, weak evidence that central stimulants such as dexamfetamine may cause or exacerbate tics or Tourette's syndrome (see under Dexamfetamine, p. 2320.2, for further details). Data for the selective noradrenaline reuptake inhibitor atomoxetine, suggests that it does not worsen tics, and may be used in patients with attention deficit hyperactivity disorder (ADHD) and comorbid motor tics or Tourette's disorder.[1] Nonetheless, there have been individual cases reported.

Health Canada[2] had received a report of tics and another of exacerbation of tics suspected of being associated with atomoxetine. In the first case, a 7-year-old girl receiving atomoxetine for ADHD had new-onset motor tics after the dose was increased to 40 mg daily; the tics persisted, but were less severe, when the dose was reduced to 25 mg daily. After risperidone was added to the regimen, the tics disappeared. The second case described exacerbation of vocal tics in an 11-year-old boy given atomoxetine 60 mg daily for ADHD; he also had Tourette's syndrome. The dose was reduced to 40 mg daily, but he continued to have tics.

1. Allen AJ, *et al.* Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurology* 2005; 65: 1941–9.
2. Health Canada. Atomoxetine (Strattera): suspected association with tics. *Can Adverse React News* 2006; 16 (4): 3. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n4-eng.php (accessed 22/01/10)

Interactions

Atomoxetine should not be taken with an MAOI, or within 2 weeks of stopping MAOI therapy, nor should MAOI therapy be started for 2 weeks after stopping atomoxetine. Care should be taken if given with other drugs that raise blood pressure, because of a possible additive effect; the actions of salbutamol on the cardiovascular system may be potentiated. In addition, there is a risk of cardiac events in patients receiving atomoxetine who are also taking drugs that affect cardiac conduction or electrolyte balance, or that inhibit the cytochrome P450 isoenzyme CYP2D6 (see below).

Seizures have been noted with atomoxetine and caution is advised when used with drugs known to lower the seizure threshold.

Atomoxetine is metabolised via the isoenzyme CYP2D6 and inhibitors of this enzyme such as paroxetine, fluoxetine, and quinidine may increase plasma concentrations of atomoxetine in extensive, but not poor, metabolisers.

Antidepressants. *Paroxetine* was found to inhibit atomoxetine's metabolism by cytochrome P450 isoenzyme CYP2D6 in extensive metabolisers resulting in pharmacokinetics for atomoxetine similar to those in poor metabolisers.[1]

1. Belle DJ, *et al.* Effect of potent CYP2D6 inhibition by paroxetine on atomoxetine pharmacokinetics. *J Clin Pharmacol* 2002; 42: 1219–27.

Pharmacokinetics

Atomoxetine is well absorbed after oral doses and peak plasma concentrations occur 1 to 2 hours later. Bioavailability is about 94% in poor metabolisers but only 63% in extensive metabolisers. Atomoxetine is about 98% bound to plasma proteins. Atomoxetine is metabolised mainly via the cytochrome P450 isoenzyme CYP2D6 to the active metabolite 4-hydroxyatomoxetine; a minority of the population are poor metabolisers and have plasma concentrations about 5 times those in extensive metabolisers. It is excreted in the urine as glucuronide metabolites and a small amount of unchanged drug; less than 17% of a dose appears in the faeces. The half-life of atomoxetine is

about 5.2 hours in extensive and 21.6 hours in poor metabolisers.

References.
1. Sauer J-M, *et al.* Clinical pharmacokinetics of atomoxetine. *Clin Pharmacokinet* 2005; 44: 571–90.
2. Cui YM, *et al.* Atomoxetine pharmacokinetics in healthy Chinese subjects and effect of the CYP2D6*10 allele. *Br J Clin Pharmacol* 2007; 64: 445–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Recit; Strattera; *Austral.*: Strattera; *Austria*: Strattera; *Belg.*: Strattera; *Canad.*: Strattera; *Chile*: Abretia; Deaten; Strattera; *China*: Strattera (择思达); *Cz.*: Strattera; *Denm.*: Strattera; *Fin.*: Strattera; *Fr.*: Strattera†; *Ger.*: Strattera; *Gr.*: Strattera; *Hong Kong*: Strattera; *Hung.*: Strattera; *India*: Attentrol; Axepta; *Irl.*: Strattera; *Ital.*: Strattera; *Jpn*: Strattera; *Malaysia*: Strattera; *Mex.*: Strattera; *Neth.*: Strattera; *Norw.*: Strattera; *NZ*: Strattera; *Philipp.*: Strattera; *Pol.*: Strattera; *Port.*: Strattera; *Rus.*: Strattera (Страттера); *S.Afr.*: Strattera; *Singapore*: Strattera; *Spain*: Strattera; *Swed.*: Strattera; *Switz.*: Strattera; *Thai.*: Strattera; *Turk.*: Strattera; *UK*: Strattera; *Ukr.*: Strattera (Страттера); *USA*: Strattera.

Pharmacopoeial Preparations
USP 36: Atomoxetine Capsules.

Bemegride *(BAN, rINN)*

Bemegrida; Bémégride; Bemegridum; Methetharimide; Бемегрид.
3-Ethyl-3-methylglutarimide; 4-Ethyl-4-methylpiperidine-2,6-dione.
$C_8H_{13}NO_2$=155.2
CAS — 64-65-3.
ATC — R07AB05.
ATC Vet — QR07AB05.
UNII — 57DQA39DO2.

Profile

Bemegride has properties similar to those of doxapram (p. 2321.2). It has been given intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Megibal.

Benzfetamine Hydrochloride *(BANM, rINNM)* ⊗

Benzfetamina, hidrocloruro de; Benzfétamine, Chlorhydrate de; Benzfetamini Hydrochloridum; Benzphetamine Hydrochloride; Hidrocloruro de benzfetamina; Бензфетамина Гидрохлорид.
(+)-*N*-Benzyl-*N*,α-dimethylphenethylamine hydrochloride.
$C_{17}H_{21}N,HCl$=275.8
CAS — 156-08-1 (benzfetamine); 5411-22-3 (benzfetamine hydrochloride).
UNII — 43DWT87QT7.

Profile

Benzfetamine hydrochloride is a central stimulant and sympathomimetic with properties similar to those of dexamfetamine (p. 2319.1). It has been used as an anorectic in the treatment of obesity (p. 2315.1), although amfetamines are no longer recommended for this indication. The usual initial oral dose is 25 to 50 mg given once daily, subsequently adjusted according to response, to a dose of 25 to 50 mg up to three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Didrex; Regimex.

Benzylpiperazine ⊗

1-Benzylpiperazine; *N*-Benzylpiperazine; Бензилпиперазин.
1-(Phenylmethyl)piperazine.
$C_{11}H_{16}N_2$=176.3
CAS — 2759-28-6.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of benzylpiperazine:
A2; Blast; BZP; Charge; Charlie; Cosmic Kelly; ESP; Euphoria; Exodus; Frenzy; Herbal ecstasy; Legal E; Legal X; Nemesis; Pep; Pep Love; Pep Stoned; Pep Twisted; Rapture; Red Eye; The Good Stuff.

Profile

Benzylpiperazine is reported to produce CNS stimulant effects similar to those of the amfetamines (see Dexamfetamine, p. 2319.1) and is subject to abuse.

Other piperazine derivatives subject to abuse include:
- 1-(3,4-methylenedioxybenzyl)piperazine (MDBP)
- 1-(3-trifluoromethylphenyl)piperazine (TFMPP)
- 1-(3-chlorophenyl)piperazine (mCPP)—NOTE: Do not confuse with MCPP, which has been used as an abbreviation for the pesticide Mecoprop
- 1-(4-methoxyphenyl)piperazine (MeOPP)

References.
1. Gee P, *et al.* Toxic effects of BZP-based herbal party pills in humans: a prospective study in Christchurch, New Zealand. *N Z Med J* 2005; 118: U1784.
2. Staack RF. Piperazine designer drugs of abuse. *Lancet* 2007; 369: 1411–13.
3. Johnstone AC, *et al.* Benzylpiperazine: a drug of abuse? *J Psychopharmacol* 2007; 21: 888–94.
4. Wood DM, *et al.* Collapse, reported seizure—and an unexpected pill. *Lancet* 2007; 369: 1490.

Bromantan ⊗

N-(2-Adamantyl)-4-bromoaniline; Bromantane.
N-(4-Bromophenyl)tricyclo[3.3.1.1^{3,7}]decan-2-amine.
$C_{16}H_{20}BrN$=306.2
CAS — 87913-26-6.

Profile

Bromantan is reported to be a stimulant that may be subject to abuse in sport. It is also reported to have immunostimulant properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Ladasten (Ладастен).

Catha ⊗

Abyssinian, African, or Arabian Tea; Kat; Kath; Khat; Miraa; Qat; Somali Tea; Té abisinio; Té de Arabia; Кат.
UNII — 57O5451KGF (Catha edulis); E14P64525U (Catha edulis leaf).

Description. Catha consists of the leaves of *Catha edulis* (Celastraceae), and contains cathine, cathinone, celastrin, choline, tannins, and inorganic salts.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of catha:
Cat; Chat; Feline; Kat; Miraa; Pootie; Qat; Quaadka.

Cathine *(pINN)* ⊗

Cathinum; Catina; (+)-Norpseudoephedrine; Катин.
threo-2-Amino-1-phenylpropan-1-ol.
$C_9H_{13}NO$=151.2
CAS — 492-39-7; 36393-56-3.
ATC — A08AA07.
ATC Vet — QA05AA07.
UNII — E1L4ZW2F8O.

Cathinone *(pINN)* ⊗

Cathinonum; Catinona; Катинон.
(*S*)-2-Aminopropiophenone.
$C_9H_{11}NO$=149.2
CAS — 71031-15-7.
UNII — 540E14406J.

Profile

Catha, the leaves of *Catha edulis* (Celastraceae), is used for its stimulant properties among some cultures of Africa and the Middle East, usually by chewing the leaves. Its effects are reported to resemble those of the amfetamines (see Dexamfetamine Sulfate, p. 2319.1), and are thought to be largely due to the content of cathinone. Dependence, cardiovascular complications, hepatotoxicity, and psychotic reactions have been reported. Derivatives of cathinone are also subject to abuse for their stimulant effects. Cathine, another constituent of catha, has been used as the hydrochloride as an anorectic.

References to the pharmacology and pharmacokinetics of catha and its constituents[1-8] and reports of adverse effects.[9-21]

1. Brenneisen R, *et al.* Metabolism of cathinone to (-)-norephedrine and (-)-norpseudoephedrine. *J Pharm Pharmacol* 1986; 38: 298–300.
2. Brenneisen R, *et al.* Amphetamine-like effects in humans of the khat alkaloid cathinone. *Br J Clin Pharmacol* 1990; 30: 825–8.
3. Kalix P. Pharmacological properties of the stimulant khat. *Pharmacol Ther* 1990; 48: 397–416.
4. Kalix P. Chewing khat, an old drug habit that is new in Europe. *Int J Risk Safety Med* 1992; 3: 143–56.
5. Kalix P. Cathinone, a natural amphetamine. *Pharmacol Toxicol* 1992; 70: 77–86.
6. Widler P, *et al.* Pharmacodynamics and pharmacokinetics of khat: a controlled study. *Clin Pharmacol Ther* 1994; 55: 556–62.
7. Kalix P. Catha edulis, a plant that has amphetamine effects. *Pharm World Sci* 1996; 18: 69–73.
8. Toennes SW, *et al.* Pharmacokinetics of cathinone, cathine and norephedrine after the chewing of khat leaves. *Br J Clin Pharmacol* 2003; 56: 125–30.
9. Rumpf KW, *et al.* Rhabdomyolysis after ingestion of an appetite suppressant. *JAMA* 1983; 250: 2112.
10. Gough SP, Cookson IB. Khat-induced schizophreniform psychosis in UK. *Lancet* 1984; i: 455.
11. Roper JP. The presumed neurotoxic effects of Catha edulis—an exotic plant now available in the United Kingdom. *Br J Ophthalmol* 1986; 70: 779–81.
12. Zuretkat N, *et al.* Chewing khat slows the orocaecal transit time. *Gut* 1992; 33 (suppl): S23.
13. Yousef G, *et al.* Khat chewing as a cause of psychosis. *Br J Hosp Med* 1995; 54: 322–6.
14. Al-Motarreb A, *et al.* Khat chewing and acute myocardial infarction. *Heart* 2002; 87: 279–280.
15. Al-Motarreb A, *et al.* Khat chewing is a risk factor for acute myocardial infarction: a case-control study. *Br J Clin Pharmacol* 2005; 59: 574–81.
16. Chapman MH, *et al.* Severe, acute liver injury and khat leaves. *N Engl J Med* 2010; 362: 1642–4.
17. Al-Motarreb A, *et al.* Khat chewing, cardiovascular diseases and other internal medical problems: the current situation and directions for future research. *J Ethnopharmacol* 2010; 132: 540–8.
18. Ali WM, *et al.* Association of khat chewing with increased risk of stroke and death in patients presenting with acute coronary syndrome. *Mayo Clin Proc* 2010; 85: 974–80.
19. Colzato LS, *et al.* Khat use is associated with impaired working memory and cognitive flexibility. *PLoS One* 2011; 6: e20602.
20. Roelandt P, *et al.* Acute liver failure secondary to khat (Catha edulis)-induced necrotic hepatitis requiring liver transplantation: case report. *Transplant Proc* 2011; 43: 3493–5.
21. Ali WM, *et al.* Acute coronary syndrome and khat herbal amphetamine use: an observational report. *Circulation* 2011; 124: 2681–9.

Abuse. Several cathinone derivatives have been synthesised and are subject to abuse for their CNS stimulant effects;[1-4] compounds include:
- butylone
- dimethylcathinone (see Metamfepramone, p. 2557.2)
- ethcathinone
- ethylone
- 3-fluoromethcathinone
- 4-fluoromethcathinone (flephedrone)
- methcathinone (ephedrone, see p. 2325.1)
- 4-methoxymethcathinone (methedrone)
- 4-methylmethcathinone (see Mephedrone, p. 2325.2)
- 3,4-methylenedioxymethcathinone (methylone)
- 3,4-methylenedioxypyrovalerone (MDPV)
- naphyrone (see p. 2328.2)
- pyrovalerone

Synthetic cathinones are often described as bath salts or plant food in order to disguise their intended use. In large doses the adverse effects of cathinone and related compounds resemble those of the amfetamines (see Dexamfetamine, p. 2319.2).

1. Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol* 2012; 8: 33–42.
2. Mas-Morey P, *et al.* Clinical toxicology and management of intoxications with synthetic cathinones ("Bath Salts"). *J Pharm Pract* 2012; 26: 353–7.
3. Ross EA, *et al.* Psychoactive "bath salts" intoxication with methylenedioxypyrovalerone. *Am J Med* 2012; 125: 854–8.
4. Baumann MH, *et al.* Psychoactive "bath salts": not so soothing. *Eur J Pharmacol* 2013; 698: 1–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Alvalin; Antiadipositum X-112 T†; *S.Afr.*: Dietene; Betless; Leanor; Nobese No. 1; Reli Slim; Slim 'n Trim; Thinz; *Thai.*: Mirapront N.

Multi-ingredient Preparations. *Mex.*: Redotex NF; Redotex.

Clobenzorex Hydrochloride *(rINNM)* ⊗

Clobenzorex, Chlorhydrate de; Clobenzorex, hidrocloruro de; Clobenzorexi Hydrochloridum; Hidrocloruro de clobenzorex; SD-271-12; Клобензорекса Гидрохлорид.
(+)-*N*-(2-Chlorobenzyl)-α-methylphenethylamine hydrochloride.
$C_{16}H_{18}ClN,HCl$=296.2
CAS — 13364-32-4 (clobenzorex); 5843-53-8 (clobenzorex hydrochloride).
ATC — A08AA08.
ATC Vet — QA08AA08.
UNII — BC6X5MB664.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of clobenzorex:
Dinintels.

Profile

Clobenzorex hydrochloride is a central stimulant and sympathomimetic with properties similar to those of dexamfetamine (p. 2319.1). It has been used as an anorectic

in the treatment of obesity but regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Asenlix; Itravil†; Obeclox; Redicres.

Deanol *(BAN)* ⊗

Démanol; Динол.
2-Dimethylaminoethanol.
$C_4H_{11}NO$=89.14
CAS — 108-01-0 (deanol); 3342-61-8 (deanol aceglumate); 3635-74-3 (deanol acetamidobenzoate); 968-46-7 (deanol benzilate); 71-79-4 (deanol benzilate hydrochloride); 15585-86-1 (deanol cyclohexylpropionate); 5988-51-2 (deanol tartrate).
ATC — N06BX04.
ATC Vet — QN06BX04.
UNII — 2N6K9DRA24.

NOTE. Deanol Aceglumate is *pINN*.

Profile

Deanol, a precursor of choline, may enhance central acetylcholine formation. It has been used as a central stimulant in the treatment of hyperactivity in children but its efficacy is not proven. It has been included in preparations used as tonics and for the management of impaired mental function.

It has been used as a variety of salts and esters including deanol aceglumate, deanol acetamidobenzoate, deanol bisorcate, deanol cyclohexylpropionate (cyprodenate; cyprodemanol), deanol glutamate, deanol hemisuccinate, deanol orotate, deanol pidolate, and deanol tartrate. Deanol benzilate (deanol diphenylglycolate; benzacine) has been used as the hydrochloride in antispasmodic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: DM Active; *Fr.*: Cleregil†; *Ger.*: Risatarun†; *Pol.*: Bimanol†; *Rus.*: Noodlerin (Нооклерин).

Multi-ingredient Preparations. *Arg.*: Pharmaton Complex; *Austria*: Vita-Gerin; *Chile*: Bedovit Pharmaton; Fortavil; Tonopron Ginseng; Ultrac B; Ultrac Cz.: Geriavit; *Fr.*: Acti 5; Debrumyl; *Ger.*: Vita-Gerin N; *Gr.*: Doprene; Pharmaton Geriatric; *Hung.*: Pharmaton Vital; *Indon.*: Pharmaton Formula; *Mex.*: Pharmaton Complex; *Philipp.*: K-A Plus; Pharmaton; Rogin-E; *Pol.*: Geriavit†; Geronpol†; *Port.*: Actilam; Debrumyl; Forticol; Tonice; Tonice; *Rus.*: Geriavit (Гериавит)†; Vitamax (Витамакс)†; *S.Afr.*: Gericomplex†; *Spain*: Anti-Anorex Triple; Denubil; Pharmaton Complex†; *Switz.*: Pharmaton Vital Geriavit; Vita-Gerin; *Thai.*: Pharmaton; *Ukr.*: Energin (Энергин); *Venez.*: Energyvit.

Dexamfetamine Sulfate *(BANM, pINNM)* ⊗

Deksamfetamin Sülfat; Dexamfétamine, Sulfate de; Dexamfetamine Sulphate; Dexamfetamini Sulfas; Dexamphetamine Sulphate; Dexamphetamini Sulfas; Dexanfetamina, sulfato de; Dextro Amphetamine Sulphate; Dextroamphetamine Sulfate; NSC-73713 (dexamfetamine); Sulfato de dexanfetamina; Дексамфетамина Сульфат.
(*S*)-α-Methylphenethylammonium sulphate; (+)-α-Methylphenethylamine sulphate.
$(C_9H_{13}N)_2H_2SO_4$=368.5
CAS — 51-64-9 (dexamfetamine); 7528-00-9 (dexamfetamine phosphate); 51-63-8 (dexamfetamine sulfate).
ATC — N06BA02.
ATC Vet — QN06BA02.
UNII — JJ768O327N.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dexamfetamine:

Dex; Dexies; Dexy; Oranges; Panama; Peaches.

Pharmacopoeias. In *Br.*, *Swiss*, and *US*.

BP 2014: (Dexamfetamine Sulfate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether.

USP 36: (Dextroamphetamine Sulfate). A white, odourless, crystalline powder. Soluble in water; slightly soluble in alcohol; insoluble in ether. pH of a 5% solution in water is between 5.0 and 6.0.

Uses and Administration

Dexamfetamine, the dextrorotatory isomer of amfetamine, is an indirect-acting sympathomimetic with alpha- and beta-adrenergic agonist activity. It has a marked stimulant effect on the CNS, particularly the cerebral cortex.

Dexamfetamine is used in the treatment of narcolepsy (p. 2314.3). It is also used in the treatment of attention deficit hyperactivity disorder (see Hyperactivity, p. 2314.1); the UK licensed product information limits its use to children with refractory hyperactivity disorders. Dexamfetamine has been given in the treatment of obesity, although amfetamines are no longer recommended for this indication. Amfetamines have also been used to overcome fatigue but, again, such use is considered undesirable. In some countries dexamfetamine has been tried for motion sickness, but safer drugs are available.

Dexamfetamine is generally used as the sulfate and is given orally.

In the treatment of **narcolepsy**, the usual initial dose is 5 to 10 mg daily in divided doses, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily. The lower initial dose of 5 mg daily is recommended for children aged 6 to 12 years and the elderly; any weekly increments should also be restricted to 5 mg in these patients.

In children with **hyperactivity** individualisation of treatment is especially important. Children aged 6 years and over usually start with a dose of 5 mg once or twice daily; the dose may be increased if necessary by 5 mg at weekly intervals to an upper limit of 20 mg daily, although older children might require up to 40 mg or more daily. Dexamfetamine is licensed for the treatment of children younger than 6 years of age in some countries, including the UK and the USA; however, many authorities consider that stimulants should not be used in young children. In the UK NICE suggests that adults may be given initial doses of 5 mg twice daily, increased according to response to a maximum of 60 mg daily.

A modified-release, combination preparation containing dexamfetamine sulfate and saccharate, with amfetamine sulfate and amfetamine aspartate monohydrate (*Adderall XR, Shire*) is also available for the treatment of attention deficit hyperactivity disorder in adults and children. In children aged 6 years and older, it is given orally as for dexamfetamine in initial doses of 10 mg of total amfetamine salts once daily increased gradually, at weekly intervals, to a maximum of 30 mg daily; in older children aged 13 to 17 years the dose may be increased to 20 mg once daily after 1 week if necessary. The initial dose in adults is 20 mg of total amfetamine salts once daily.

Administration in children. For doses of dexamfetamine in children and adolescents, see Uses and Administration, above.

Adverse Effects

The adverse effects of dexamfetamine are commonly symptoms of overstimulation of the CNS and include insomnia, night terrors, nervousness, restlessness, irritability, and euphoria that may be followed by fatigue and depression. There may be dryness of the mouth, anorexia, abdominal cramps and other gastrointestinal disturbances, headache, dizziness, tremor, sweating, tachycardia, palpitations, myocardial infarction, increased or sometimes decreased blood pressure, altered libido, and impotence. Psychotic reactions, such as hallucinations and delusional thinking, mania, seizures, and stroke have occurred, as has muscle damage with associated rhabdomyolysis and renal complications. Rarely, cardiomyopathy has occurred with chronic use. Sudden death has been reported in patients with structural cardiac abnormalities (see also Effects on the Cardiovascular System, below). In addition in children, growth retardation may occur during prolonged treatment.

In *acute overdosage*, the adverse effects are accentuated and may be accompanied by hyperpyrexia, mydriasis, hyperreflexia, chest pain, cardiac arrhythmias, confusion, panic states, aggressive behaviour, hallucinations, delirium, convulsions, respiratory depression, coma, circulatory collapse, and death. Individual patient response may vary widely and toxic manifestations may occur with quite small overdoses.

Tolerance can develop to some of dexamfetamine's central effects leading to increased doses and habituation. Abrupt cessation after prolonged treatment or abuse of amfetamines has been associated with extreme fatigue, hyperphagia, and depression. However, it is generally accepted that the amfetamines, although widely abused, are not associated with substantial physical dependence.

Abuse of amfetamines for their euphoriant effects has resulted in personality changes, compulsive and stereotyped behaviour, and may induce a toxic psychosis with auditory and visual hallucinations and paranoid delusions.

Abuse. Abuse of amfetamines can lead to toxicity affecting many organs or body systems. There have been reports of *intracerebral haemorrhage*[1-3] and of *cardiomyopathy*.[4-6] *Acute myocardial infarction* has also occurred.[7]

A syndrome characterised by *circulatory collapse, fever, leukaemoid reaction, disseminated intravascular coagulation*, and *rhabdomyolysis* with *diffuse myalgias* and *muscle tenderness* has been described[8] in 5 drug abusers who had used amfetamines or phenmetrazine intravenously. In an earlier study,[9] *necrotising angiitis* was associated with intravenous metamfetamine abuse. A 30-year-old man who had ingested 50 amfetamine sulfate tablets developed *rhabdomyolysis* and *myoglobinuric renal failure*, possibly secondary to a crush syndrome, but in the absence of prolonged coma or other major myotoxic factors.[10] However, *acute interstitial nephritis* and *acute renal failure* have followed oral amfetamine abuse without the associated factors of rhabdomyolysis, hyperpyrexia, or necrotising angiitis.[11] *Hyperglycaemia* has also been noted after the recreational abuse of dexamfetamine tablets.[12]

Chronic use may result in adverse effects such as *hallucinations*, a *delusional disorder* resembling *paranoid schizophrenia, stereotyped behaviour*, and *movement disorders*.[13] Although chronic intoxication is the most common precondition for psychosis, individual sensitivities are an important aspect of the drug reaction.

Increased serum concentrations of *levothyroxine* have been associated with heavy amfetamine abuse in 4 psychiatric patients.[14]

Abrupt cessation after prolonged treatment or abuse of amfetamines may cause *extreme fatigue, hyperphagia*, and *depression*. *Depressive stupor* has been reported in 3 long-term abusers of amfetamine after sudden withdrawal.[15]

1. Delaney P, Estes M. Intracranial hemorrhage with amphetamine abuse. *Neurology* 1980; 30: 1125–8.
2. Harrington H, *et al.* Intracerebral hemorrhage and oral amphetamine. *Arch Neurol* 1983; 40: 503–7.
3. Salanova V, Taubner R. Intracerebral haemorrhage and vasculitis secondary to amphetamine use. *Postgrad Med J* 1984; 60: 429–30.
4. Smith EJ, *et al.* Cardiomyopathy associated with amphetamine administration. *Am Heart J* 1976; 91: 792–7.
5. Call TD, *et al.* Acute cardiomyopathy secondary to intravenous amphetamine abuse. *Ann Intern Med* 1982; 97: 559–60.
6. Hong R, *et al.* Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA* 1991; 265: 1152–4.
7. Waksman J, *et al.* Acute myocardial infarction associated with amphetamine use. *Mayo Clin Proc* 2001; 76: 323–6.
8. Kendrick WC, *et al.* Rhabdomyolysis and shock after intravenous amphetamine administration. *Ann Intern Med* 1977; 86: 381–7.
9. Citron BP, *et al.* Necrotizing angiitis associated with drug abuse. *N Engl J Med* 1970; 283: 1003–11.
10. Scandling J, Spital A. Amphetamine-associated myoglobinuric renal failure. *South Med J* 1982; 75: 237–40.
11. Poley RJ, *et al.* Amphetamine-induced acute renal failure. *South Med J* 1984; 77: 258–60.
12. Henley DE, Glatthaar C. ADHD: a diabetic hyperglycemic dilemma. *Diabetes Care* 2004; 27: 3020–1.
13. Ellinwood EH, Kilbey MM. Fundamental mechanisms underlying altered behavior following chronic administration of psychomotor stimulants. *Biol Psychiatry* 1980; 15: 749–57.
14. Morley JE, *et al.* Amphetamine-induced hyperthyroxinemia. *Ann Intern Med* 1980; 93: 707–9.
15. Tuma TA. Depressive stupor following amphetamine withdrawal. *Br J Hosp Med* 1993; 49: 361–3.

Effects on the cardiovascular system. There have been very rare reports of sudden death in children and adults taking *Adderall* (*Shire*), a combination preparation of amfetamine salts. In February 2005 Health Canada[1] reported that, worldwide, there have been 20 cases of sudden death in patients taking the product at usual recommended doses; 14 of these deaths occurred in children. In some cases there was no history of cardiac disorders nor any structural abnormalities. Health Canada considered the incidence of fatal adverse effects to be greater with this combination preparation than with other stimulants and consequently withdrew the product from the Canadian market. However, a subsequent independent review committee recommended[2] that *Adderall* be allowed back onto the Canadian market although they did warn that it should not be used in patients with structural cardiac abnormalities.[3]

The committee also recommended that all stimulants used in ADHD undergo enhanced postmarketing surveillance and consequently, in May 2006, Health Canada[4] revised the labelling of amfetamine, atomoxetine, dexamfetamine, dexmethylphenidate, and methylphenidate to include warnings about their effects on the cardiovascular system. However, it was also noted that the incidence or reporting rates of serious cardiovascular adverse effects with these drugs, including fatal cases, were no greater than background rates. (Similar changes have since been made in the labelling of these products in other countries.)

In June 2009, the FDA[5] commented on a case-control study[6] that had found an association between the use of stimulants and sudden death in healthy children and adolescents. The FDA[5] was unable to conclude that the data from this study had affected the overall risk to benefit ratio of stimulants because of the study's limitations in methodology; they advised that stimulant medication should not be stopped on the basis of this study. Prescribers

were reminded to screen children for cardiovascular disease, including family history, and to consider obtaining further tests if there is an underlying risk for, or presence of, heart disease. A review of the use of stimulants for ADHD in children is ongoing.

1. Health Canada. Health Canada has suspended market authorization of ADDERALL XR® (amphetamine salts), a drug approved for Attention Deficit Hyperactivity Disorder (ADHD) in children (issued 9th February, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/adderall_xr_hpc-cps-eng.pdf (accessed 11/08/08)
2. Health Canada. Report of the "Adderall XR New Drug Committee" (issued 26th August, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ndca_rep_cnma_rap_2005-08-25-eng.pdf (accessed 11/08/08)
3. Shire, Canada. ADDERALL XR and serious adverse events (issued 31st August, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/adderall_xr2_hpc-cps-eng.pdf (accessed 11/08/08)
4. Health Canada. Attention deficit hyperactivity disorder (ADHD) drugs: updated and standardized labelling regarding very rare cardiac-related adverse events (issued May 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/adhd-rdah_medic_hpc-cps_e.pdf (accessed 21/09/06)
5. FDA. Communication about an ongoing safety review of stimulant medications used in children with attention-deficit/hyperactivity disorder (ADHD) (issued 23rd June, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165858.htm (accessed 25/06/09)
6. Gould MS, *et al.* Sudden death and use of stimulant medications in youths. *Am J Psychiatry* 2009; 166: 922–1001.

Effects on growth. The Pediatric Subcommittee of the FDA Psychopharmacologic Drugs Advisory Committee reviewed the growth-suppressing effects of stimulant medication (dextroamfetamine, methylphenidate, and pemoline) in hyperkinetic children.[1] There was reasonable evidence that stimulant drugs, particularly in higher doses, moderately suppressed growth in weight and might have a minor suppressing effect on growth in stature. There were indications that some growth caught up during drug holidays, and that early growth suppression was not evident in adulthood. Careful monitoring during treatment was recommended.

See also under Methylphenidate Hydrochloride, p. 2327.1.

1. Roche AF, *et al.* The effects of stimulant medication on the growth of hyperkinetic children. *Pediatrics* 1979; 63: 847–50.

Treatment of Adverse Effects

Activated charcoal may be given to delay absorption if the patient presents within 1 hour of ingesting any amount of an amfetamine; however, the benefit of gastric decontamination is uncertain. In general the management of overdosage with amfetamines involves supportive and symptomatic therapy. Sedation is usually sufficient. Forced acid diuresis has been used to increase amfetamine excretion in severely poisoned patients but is seldom necessary; it requires close supervision and monitoring.

Precautions

Dexamfetamine is contra-indicated in patients with cardiovascular disease including moderate to severe hypertension and those with structural cardiac abnormalities, cardiomyopathy, or advanced arteriosclerosis. It should also not be used in patients with hyperthyroidism, glaucoma, hyperexcitability, or agitated states. Dexamfetamine should not be given to those with a history of drug or alcohol abuse and it should be avoided in pregnant or breast-feeding women.

It should be given with caution to patients with mild hypertension, renal impairment, bipolar disorder, or unstable personality. Behavioural disturbances and thought disorders may be exacerbated in psychotic patients.

Height and weight in children should be monitored as growth retardation may occur.

Care may be needed in certain patients predisposed to tics or Tourette's syndrome as symptoms may be provoked. Dexamfetamine is likely to reduce the convulsive threshold; caution is therefore advised in patients with epilepsy. However, it appears that in some countries amfetamines have been included in antiepileptic preparations containing phenytoin or phenobarbital in an attempt to increase their antiepileptic action. Amfetamines may impair patients' ability to drive or to operate machinery.

It was recommended that diabetic control should be monitored when central stimulants were used for the control of obesity, but dexamfetamine is no longer licensed for this indication.

Prolonged high doses may need gradual withdrawal as abrupt cessation may produce fatigue and mental depression.

Abuse. Dexamfetamine is subject to extensive abuse and for this reason its availability is severely curtailed. For adverse effects associated with abuse, see p. 2319.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dexamfetamine 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 25/10/11)

Pregnancy. No difference was found in the incidence of severe congenital anomalies between 1824 children of mothers prescribed amfetamines or phenmetrazine during pregnancy and 8989 children of mothers not given these drugs.[1] Though an excess of oral clefts was noted in the offspring of mothers prescribed amfetamines, there was no excess of congenital heart disease.[1] This was contrary to a previous suggestion[2] in which congenital heart disease in 184 infants had been studied and a link to maternal dexamfetamine exposure postulated. There has been a report of a bradycardia followed by death in a fetus due to maternal intravenous self-administration of 500 mg of amfetamine.[3]

1. Milkovich L, van den Berg BJ. Effects of antenatal exposure to anorectic drugs. *Am J Obstet Gynecol* 1977; 129: 637–42.
2. Nora JJ, *et al.* Dexamphetamine: a possible environmental trigger in cardiovascular malformations. *Lancet* 1970; i: 1290–1.
3. Dearlove JC, Betteridge TJ. Stillbirth due to intravenous amphetamine. *BMJ* 1992; 304: 548.

Tourette's syndrome. A review[1] of clinical reports concluded that there was virtually no evidence that central stimulants caused or provoked Tourette's syndrome and weak or inadequate evidence that clinically appropriate doses of central stimulants caused tics in previously asymptomatic patients or exacerbated pre-existing symptoms. However, the authors suggested that there was evidence that high or toxic doses might exacerbate or provoke tics in predisposed patients. Long-term methylphenidate therapy did not appear to exacerbate motor or vocal tics in a study[2] of 34 children with ADHD and chronic multiple tic disorder who were followed up for 2 years. However, the authors did point out that careful clinical monitoring is essential to eliminate the possibility of drug-induced exacerbation in individual patients. In contrast, a report[3] on 15 children who developed Tourette's syndrome while receiving stimulant medication for hyperactivity considered that such therapy was contra-indicated in children with motor tics or diagnosed Tourette's syndrome; it should also be used with caution in children with a family history of these symptoms. In addition, it suggested that the development of motor tic symptoms in any child given stimulants should be a clear indication for stopping immediately to minimise the possibility of eliciting a full-blown Tourette's syndrome.

1. Shapiro AK, Shapiro E. Do stimulants provoke, cause, or exacerbate tics and Tourette syndrome? *Compr Psychiatry* 1981; 22: 265–73.
2. Gadow KD, *et al.* Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Arch Gen Psychiatry* 1999; 56: 330–6.
3. Lowe TL, *et al.* Stimulant medications precipitate Tourette's syndrome. *JAMA* 1982; 247: 1729–31.

Interactions

Dexamfetamine is an indirect-acting sympathomimetic and may interact with many other drugs. To avoid precipitating a hypertensive crisis, it should not be given to patients being treated with an MAOI or within 14 days of stopping such treatment. Use of beta blockers with amfetamines may produce severe hypertension. Dexamfetamine may also diminish the effects of other antihypertensives, including guanethidine and similar drugs, and concurrent use should be avoided. Patients receiving amfetamines and tricyclic antidepressants require careful monitoring as the risk of cardiovascular effects including arrhythmias may be increased. The urinary excretion of amfetamines is reduced by urinary alkalinisers, which may enhance or prolong their effects; excretion is increased by urinary acidifiers.

Amfetamines may delay the absorption of ethosuximide, phenobarbital, and phenytoin. The stimulant effects of amfetamines are inhibited by chlorpromazine, haloperidol, and lithium. Disulfiram may inhibit the metabolism and excretion of amfetamines.

Use of sympathomimetics with volatile liquid anaesthetics such as halothane is associated with an increased risk of cardiac arrhythmias.

Pharmacokinetics

Amfetamines are readily absorbed from the gastrointestinal tract and are distributed into most body tissues with high concentrations in the brain and CSF. They are partially metabolised in the liver but a considerable fraction may be excreted in the urine unchanged. Urinary elimination is pH-dependent and enhanced in acid urine. Amfetamines are distributed into breast milk.

References.

1. Steiner E, *et al.* Amphetamine secretion in breast milk. *Eur J Clin Pharmacol* 1984; 27: 123–4.
2. de la Torre R, *et al.* Clinical pharmacokinetics of amfetamine and related substances: monitoring in conventional and non-conventional matrices. *Clin Pharmacokinet* 2004; 43: 157–85.
3. Ilett KF, *et al.* Transfer of dexamphetamine into breast milk during treatment for attention deficit hyperactivity disorder. *Br J Clin Pharmacol* 2007; 63: 371–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Dexedrine; *UK*: Dexedrine†; *USA*: Dexedrine; Dextrostat; Liquadd†; ProCentra; Zenzedi.

Multi-ingredient Preparations. *Canad.*: Adderall; *USA*: Adderall; MAS-ER.

Pharmacopoeial Preparations
BP 2014: Dexamfetamine Tablets.

Dexfenfluramine Hydrochloride

(BANM, USAN, rINNM) ⊗

Deksfenfluramiinihydrokloridi; Dexfenfluramina, hidrocloruro de; Dexfenfluramine, Chlorhydrate de; Dexfenfluraminhydroklorid; Dexfenfluramini Hydrochloridum; Hidrocloruro de dexfenfluramina; S-5614 (dexfenfluramine); Дексфенфлурамина Гидрохлорид.

(*S*)-*N*-Ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride.

$C_{12}H_{16}F_3N$,HCl=267.7

CAS — 3239-44-9 (dexfenfluramine); 3239-45-0 (dexfenfluramine hydrochloride).

ATC — A08AA04.

ATC Vet — QA08AA04.

UNII — PM28L0FHNP.

Profile

Dexfenfluramine is the *S*-isomer of fenfluramine (p. 2322.3). It stimulates the release of serotonin and selectively inhibits its reuptake, but differs from fenfluramine in not possessing any catecholamine agonist activity.

Dexfenfluramine was formerly given orally as the hydrochloride in the treatment of obesity but, like fenfluramine, was withdrawn worldwide after reports of valvular heart defects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Isomeran.

Dexmethylphenidate Hydrochloride

(USAN, rINNM) ⊗

d-MPH; Dexméthylphénidate, Chlorhydrate de; Dexmethylphenidati Hydrochloridum; Dexmetilfenidato, hidrocloruro de; *d-threo*-Methylphenidate; Hidrocloruro de dexmetilfenidato; *d*-Methylphenidate Hydrochloride; Дексметилфенидата Гидрохлорид.

Methyl (2*R*)-phenyl[(2*R*)-piperidin-2-yl]acetate hydrochloride.

$C_{14}H_{19}NO_2$,HCl=269.8

CAS — 40431-64-9 (dexmethylphenidate); 19262-68-1 (dexmethylphenidate hydrochloride).

ATC — N06BA11.

ATC Vet — QN06BA11.

UNII — 1678OK0E08.

NOTE. The name Attenade has been used as a trade mark for dexmethylphenidate.

Profile

Dexmethylphenidate hydrochloride is the *d-threo*-enantiomer of racemic methylphenidate hydrochloride (p. 2326.1). It is given orally as a central stimulant in the treatment of attention deficit hyperactivity disorder (see Hyperactivity, p. 2314.1).

Dexmethylphenidate hydrochloride is licensed for use in children aged 6 years and older. For patients new to methylphenidate the starting dose of dexmethylphenidate hydrochloride is 2.5 mg twice daily. Each dose should be given at least four hours apart. Dosage may be adjusted in 2.5 to 5 mg increments weekly to a maximum of 10 mg twice daily.

For patients currently using methylphenidate the starting dose of dexmethylphenidate hydrochloride is half the dose of the racemic substance. The maximum recommended dose is 10 mg twice daily.

A modified-release formulation is also available for once-daily dosing.

Dexmethylphenidate should be stopped if there is no improvement in symptoms after appropriate adjustments in dosage over one month. It also needs to be stopped from time to time in those who do respond to assess the patient's condition.

References.
1. Robinson DM, Keating GM. Dexmethylphenidate extended release: in attention-deficit hyperactivity disorder. *Drugs* 2006; 66: 661–8.
2. Coury D. Dexmethylphenidate for attention deficit hyperactivity disorder. *Expert Opin Pharmacother* 2009; 10: 2679–85.
3. Moen MD, Keam SJ. Dexmethylphenidate extended release: a review of its use in the treatment of attention-deficit hyperactivity disorder. *CNS Drugs* 2009; 23: 1057–83.

Administration in children. For doses of dexmethylphenidate hydrochloride in children and adolescents, see p. 2320.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Switz.*: Focalin; *USA*: Focalin.

Diethylaminoethanol ⊗

Dietilaminoetanol; Диэтиламиноэтанол.
2-Diethylaminoethanol.
$C_6H_{15}NO$=117.2
CAS — 100-37-8.
UNII — S6DL4M053U.

Profile

Diethylaminoethanol is an analogue of deanol (p. 2319.1) and has been used similarly as the malate. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Durobion.

Diethylpropion Hydrochloride *(BANM)* ⊗

Amfépramone, Chlorhydrate d'; Amfepramone Hydrochloride (pINNM); Amfepramoni Hydrochloridum; Anfepramona, hidrocloruro de; Hidrocloruro de anfepramona; Hidrocloruro de dietilpropión; Амфепрамона Гидрохлорид. *N*-(1-Benzoylethyl)-*NN*-diethylammonium chloride; 2-Diethylaminopropiophenone hydrochloride; (*RS*)-α-Diethylaminopropiophenone hydrochloride.
$C_{13}H_{19}NO.HCl$=241.8
CAS — 90-84-6 (diethylpropion); 134-80-5 (diethylpropion hydrochloride).
ATC — A08AA03.
ATC Vet — QA08AA03.
UNII — 19V2PL39NG.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of diethylpropion:
Blue; Blues.

Pharmacopoeias. In *US*.

USP 36: (Diethylpropion Hydrochloride). A white to off-white, fine crystalline powder. Is odourless or has a slight characteristic odour. It may contain tartaric acid as a stabilising agent. Soluble 1 in 0.5 of water, 1 in 3 of alcohol, and 1 in 2 of chloroform; practically insoluble in ether. Protect from light.

Uses and Administration

Diethylpropion hydrochloride is a central stimulant and indirect-acting sympathomimetic with the actions of dexamfetamine (p. 2319.2). It is used as an oral anorectic in the short-term treatment of obesity (p. 2315.1), although stimulants are not generally recommended for this indication.

Doses of 25 mg three times daily 1 hour before meals or 75 mg once daily in mid-morning as a modified-release preparation, are given. To reduce the risk of dependence, diethylpropion should not be given for more than a few weeks at a time.

Regulatory authorities in the EU have called for the withdrawal of diethylpropion from the market (see under Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2. In addition gynaecomastia has been reported rarely. The incidence of central adverse effects may be lower with diethylpropion than with dexamfetamine. Diethylpropion should not be given to patients with emotional instability or a history of psychiatric illness. It should be avoided in children and the elderly. Diethylpropion hydrochloride is subject to abuse.

Interactions

Diethylpropion is an indirect-acting sympathomimetic; interactions are similar to those seen with dexamfetamine (p. 2320.2).

Pharmacokinetics

Diethylpropion is readily absorbed from the gastrointestinal tract. It is extensively metabolised in the liver and possibly the gastrointestinal tract and is excreted in the urine. Diethylpropion crosses the blood-brain barrier and the placenta. Diethylpropion and its metabolites are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Tenuate†; *Braz.*: Dualid S; Hipofagin S; Inibex S; *Canad.*: Tenuate†; *Chile*: Sacin†; *Denm.*: Regenon; *Ger.*: Regenon; Tenuate Retard; *Gr.*: Linea; *Hong Kong*: Atractil; Prothin; *Mex.*: Ifa Norex†; Neobes; *NZ*: Tenuate Dospan†; *S.Afr.*: Tenuate Dospan; *Thai.*: Atractil†; Dietil†; Prefamone; *USA*: Tenuate.

Multi-ingredient Preparations. *Arg.*: Tratobes; *Indon.*: Apisate†.

Pharmacopoeial Preparations
USP 36: Diethylpropion Hydrochloride Tablets.

Dimefline Hydrochloride *(BANM, USAN, rINNM)*

Dimeflina, hidrocloruro de; Diméfline, Chlorhydrate de; Dimeflini Hydrochloridum; DW-62; Hidrocloruro de dimeflina; NSC-114650; Rec-7/0267; Димефлина Гидрохлорид. 8-Dimethylaminomethyl-7-methoxy-3-methyl-2-phenylchromen-4-one hydrochloride.
$C_{20}H_{21}NO_3.HCl$=359.8
CAS — 1165-48-6 (dimefline); 2740-04-7 (dimefline hydrochloride).
ATC — R07AB08.
ATC Vet — QR07AB08.
UNII — H0XB4R74ID.

Profile

Dimefline has actions similar to those of doxapram (below). The hydrochloride has been given orally or parenterally as a respiratory stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Fei Er (菲而); Lin Mai Xin (林迈欣); *Ital.*: Remeflin.

Doxapram Hydrochloride *(BANM, USAN, rINNM)*

AHR-619; Doksapraamihydroklóridi; Doksapram Hidroklorür; Doksapramo hidrochloridas; Doxapram, Chlorhydrate de; Doxapram, hidrocloruro de; Doxapram-hidroklorid; Doxapramhydrochlorid; Doxapram-hydrochlorid monohydrát; Doxapramhydroklorid; Doxaprami hydrochloridum; Doxaprami Hydrochloridum Monohydricum; Hidrocloruro de doxapram; Доксапрама Гидрохлорид.
1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride monohydrate.
$C_{24}H_{30}N_2O_2.HCl.H_2O$=433.0
CAS — 309-29-5 (doxapram); 113-07-5 (anhydrous doxapram hydrochloride); 7081-53-0 (doxapram hydrochloride monohydrate).
ATC — R07AB01.
ATC Vet — QR07AB01.
UNII — P5RU6UOQ5Y.

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

Ph. Eur. 8: (Doxapram Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol and in dichloromethane. A 0.4% solution in water has a pH of 3.5 to 5.0.

USP 36: (Doxapram Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 50 of water; soluble in chloroform; sparingly soluble in alcohol; practically insoluble in ether. pH of a 1% solution in water is between 3.5 and 5.0. Store in airtight containers.

Incompatibility. The commercial injection of doxapram hydrochloride is reported to be incompatible with alkaline solutions such as aminophylline, furosemide, or thiopental sodium.

Uses and Administration

Doxapram hydrochloride is a central and respiratory stimulant with a brief duration of action. It acts by stimulation of peripheral chemoreceptors and central respiratory centres; at higher doses, it stimulates other parts of the brain and spinal cord. Doxapram has a pressor action and may also increase catecholamine release.

Doxapram has limited uses in the treatment of acute respiratory failure (for example where this is superimposed on chronic obstructive pulmonary disease— below), and of postoperative respiratory depression (below).

Doxapram hydrochloride may be infused at a rate of 1.5 to 4 mg/minute in the treatment of acute respiratory failure.

For postoperative respiratory depression it has been given in a dose of 0.5 to 1.5 mg/kg by intravenous injection over a period of at least 30 seconds. This dose may be repeated at hourly intervals. It may also be given by intravenous infusion, initially at a rate of 2 to 5 mg/minute and then reduced, according to response, to 1 to 3 mg/minute; a recommended maximum total dosage is 4 mg/kg.

Doxapram hydrochloride has also been used to treat respiratory and CNS depression following drug overdose but its use for this indication is no longer recommended.

Chronic obstructive pulmonary disease. Respiratory stimulants such as doxapram have a limited and short-term role in hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease (p. 1199.1). Benefit has been reported in such patients in whom doxapram was used as an alternative to intubation.[1,2] However, a systematic review suggested that despite short-term improvements in blood-gas exchange with doxapram, techniques such as non-invasive ventilation might be more effective.[3]

1. Hirshberg AJ, *et al.* Use of doxapram hydrochloride injection as an alternative to intubation to treat chronic obstructive pulmonary disease patients with hypercapnia. *Ann Emerg Med* 1994; 24: 701–3.
2. Kerr HD. Doxapram in hypercapnic chronic obstructive pulmonary disease with respiratory failure. *J Emerg Med* 1997; 15: 513–15.
3. Greenstone M, Lasserson TJ. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 16/05/05).

Neonatal apnoea. Doxapram is effective in neonatal apnoea (p. 1204.3) and may be considered as an alternative, or in addition, to xanthines in infants with apnoea that does not respond to xanthine therapy alone. However, it is less convenient to use as it must be given by continuous intravenous infusion and blood pressure must be monitored (although it has also been suggested that the oral route may be used after the initial intravenous dose). Additionally, some preparations may contain benzyl alcohol as a preservative making them unsuitable for use in neonates (see p. 1740.1). It has been used in intravenous doses of 2.5 mg/kg per hour.[1-3] Adverse CNS effects have been reported.[3] Lower doses of 0.25 or 1.5 mg/kg per hour have been shown to be effective.[4,5] However, use of low doses of 500 micrograms/kg per hour in very low birth-weight premature infants produced higher than expected plasma-doxapram concentrations and a greater increase in systolic blood pressure compared with controls.[6] A systematic review[7] concluded that the place of doxapram in the management of neonatal apnoea had not yet been properly established.

1. Sagi E, *et al.* Idiopathic apnoea of prematurity treated with doxapram and aminophylline. *Arch Dis Child* 1984; 59: 281–3.
2. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; 75: 709–13.
3. Dear PRF, Wheeler D. Doxapram and neonatal apnoea. *Arch Dis Child* 1984; 59: 903–4.
4. Bairam A, Vert P. Low-dose doxapram for apnoea of prematurity. *Lancet* 1986; i: 793–4.
5. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; 116: 648–53.
6. Huon C, *et al.* Low-dose doxapram for treatment of apnoea following early weaning in very low birthweight infants: a randomized, double-blind study. *Acta Paediatr* 1998; 87: 1180–4.
7. Henderson-Smart DJ, Steer PA. Doxapram treatment for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 23/10/07).

Respiratory depression. References to the use of doxapram in postoperative respiratory depression (see Respiratory Failure, under Oxygen, p. 1801.1).

1. Jansen JR, *et al.* Effect of doxapram on postoperative pulmonary complications after upper abdominal surgery in high-risk patients. *Lancet* 1990; 335: 936–8.
2. Thangathurai D, *et al.* Doxapram for respiratory depression after epidural morphine. *Anaesthesia* 1990; 45: 64–5.
3. Sajjad T. Comparison of the effects of doxapram or carbon dioxide on ventilatory frequency and tidal volume during induction of anaesthesia with propofol. *Br J Anaesth* 1994; 73: 266P.
4. Alexander-Williams M, *et al.* Doxapram and the prevention of postoperative hypoxaemia. *Br J Anaesth* 1995; 75: 233P.

Shivering. Doxapram is one of several drugs that have been used in postoperative shivering (p. 1897.2).

References.
1. Sarma V, Pry ENS. Doxapram after general anaesthesia: its role in stopping shivering during recovery. *Anaesthesia* 1991; 46: 460–1.

2. Singh P, *et al.* Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. *Br J Anaesth* 1993; 71: 685–8.
3. Wrench IJ, *et al.* The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. *Anaesthesia* 1997; 52: 32–6.

Adverse Effects

As with other respiratory stimulants, there is a risk that doxapram will produce adverse effects due to general stimulation of the CNS.

Doxapram may produce dyspnoea and other respiratory problems such as coughing, bronchospasm, laryngospasm, hiccup, hyperventilation, and rebound hypoventilation. Muscle involvement may range from fasciculations to spasticity. Convulsions, headache, dizziness, hyperactivity, and confusion can occur as can sweating, flushing, fever or a sensation of warmth, particularly in the genital or perineal regions. Hallucinations may occur rarely. There may be nausea, vomiting, diarrhoea, and problems with urination. Cardiovascular effects include hypertension and various arrhythmias although sudden hypotension may also occur.

Thrombophlebitis may follow extravasation of doxapram during injection.

Effects on the heart. Second-degree AV block caused by prolongation of the QT interval has been associated with doxapram use in 3 neonates.[1] Although the preparation used contained benzyl alcohol this was not considered to play a role in the adverse effect. A prospective study[2] involving 40 premature infants given doxapram for apnoea of prematurity also found QT interval lengthening at 48 and 72 hours of treatment, even when the drug plasma concentrations were kept within therapeutic ranges. In 6 infants, the QT interval lengthened to a degree considered to be life-threatening. There was also a trend towards moderate increases in blood pressure. The authors recommended heart monitoring when doxapram was given to premature infants.

1. De Villiers GS, *et al.* Second-degree atrioventricular heart block after doxapram administration. *J Pediatr* 1998; 133: 149–50.
2. Maillard C, *et al.* QT interval lengthening in premature infants treated with doxapram. *Clin Pharmacol Ther* 2001; 70: 540–5.

Effects on the liver. Acute hepatic necrosis in a patient was attributed to a 24-hour infusion of doxapram.[1] Liver function tests returned to normal over 3 weeks.

1. Fancourt GJ, *et al.* Hepatic necrosis with doxapram hydrochloride. *Postgrad Med J* 1985; 61: 833–5.

Precautions

Doxapram should not be given to patients with epilepsy or other convulsive disorders, cerebral oedema, cerebrovascular accident, head injury, acute severe asthma, physical obstruction of the airway, severe hypertension, ischaemic heart disease, hyperthyroidism, or phaeochromocytoma. Caution is also advisable if doxapram is used in patients with less severe degrees of hypertension or impaired cardiac reserve. It should be given with care to patients with significant hepatic or renal impairment.

Patients should be carefully supervised during use of doxapram; special attention should be paid to changes in blood gas measurements. Doxapram should be given with oxygen in severe irreversible airways obstruction or severely decreased lung compliance because of the increased work of breathing. A beta$_2$ agonist should also be given to patients with bronchoconstriction.

Interactions

Additive pressor effects may occur when doxapram is used with sympathomimetics or MAOIs. Cardiac arrhythmias may occur when doxapram is given with anaesthetics known to sensitise the myocardium, such as halothane, enflurane, and isoflurane; it has been recommended that doxapram should not be given for at least 10 minutes after stopping these anaesthetics. Doxapram may temporarily mask the residual effects of neuromuscular blockers. The manufacturers have reported that there may be an interaction between doxapram and aminophylline manifested by agitation and increased skeletal muscle activity.

Pharmacokinetics

After intravenous doses doxapram is rapidly distributed into the tissues. Onset of respiratory stimulation usually occurs in 20 to 40 seconds, with a peak effect achieved in 1 to 2 minutes. Duration of effect following a single dose varies from 5 to 12 minutes. Doxapram is extensively metabolised in the liver. The major route of excretion of metabolites and a small amount of unchanged drug is thought to be via bile to the faeces. It is also excreted in the urine.

Some absorption occurs when doxapram is given orally.

References.

1. Robson RH, Prescott LF. A pharmacokinetic study of doxapram in patients and volunteers. *Br J Clin Pharmacol* 1978; 7: 81–7.
2. Baker JR, *et al.* Normal pharmacokinetics of doxapram in a patient with renal failure and hypothyroidism. *Br J Clin Pharmacol* 1981; 11: 305–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Dopram; ***China***: Boda (波达); Dai Er Song (代尔松); Jia Su Lun (佳苏仑); Ze Lun (泽仑); ***Denm.***: Dopram; ***Fin.***: Dopram; ***Fr.***: Dopram; ***Ger.***: Dopram; ***Gr.***: Dopram; ***India***: Caropram; ***Irl.***: Dopram†; ***Neth.***: Dopram; ***Norw.***: Dopram†; ***S.Afr.***: Dopram†; ***UK***: Dopram; ***USA***: Dopram.

Pharmacopoeial Preparations
BP 2014: Doxapram Injection;
USP 36: Doxapram Hydrochloride Injection.

Etamivan *(BAN, rINN)* ⊗

Etamivaani; Etamiván; Étamivan; Etamivanum; Ethamivan (USAN); Ethamivan; NSC-406087; Vanillic Acid Diethylamide; Vanillic Diethylamide; Этамиван.

N,N-Diethylvanillamide.

$C_{12}H_{17}NO_3$=223.3

CAS — 304-84-7.
ATC — R07AB04.
ATC Vet — QR07AB04.
UNII — M44O63YPV9.

Profile

Etamivan has actions similar to those of doxapram (p. 2321.2). It was formerly used as a respiratory stimulant, but the risk of toxicity associated with effective doses is now considered to be unacceptable.

Etamivan is available in oral compound preparations for cerebrovascular and circulatory disorders and hypotension, but such use is not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Dosulfin Bronquial; ***Hong Kong***: Instenon; ***Rus.***: Instenon (Инстенон); ***Ukr.***: Instenon (Инстенон).

Fencamfamin Hydrochloride *(BANM, rINNM)* ⊗

Fencamfamine, Chlorhydrate de; Fencamfamini Hydrochloridum; Fencanfamina, hidrocloruro de; H-610; Hidrocloruro de fencanfamina; Фенкамфамина Гидрохлорид.

N-Ethyl-3-phenylbicyclo[2.2.1]hept-2-ylamine hydrochloride.

$C_{15}H_{21}N,HCl$=251.8

CAS — 1209-98-9 (fencamfamin); 2240-14-4 (fencamfamin hydrochloride).
ATC — N06BA06.
ATC Vet — QN06BA06.
UNII — 0M1J608WEX.

Profile

Fencamfamin hydrochloride has been given orally as a central stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Fenetylline Hydrochloride *(BANM, rINNM)* ⊗

Amfetylline Hydrochloride; 7-Ethyltheophylline Amphetamine Hydrochloride; Fenethylline Hydrochloride (USAN); Fenethylline Hydrochloride; Fenetilina, hidrocloruro de; Fénétylline, Chlorhydrate de; Fenetyllini Hydrochloridum; H-814; Hidrocloruro de fenetilina; R-720-11; Фенетиллина Гидрохлорид.

7-[2-(α-Methylphenethylamino)ethyl]theophylline hydrochloride.

$C_{18}H_{23}N_5O_2,HCl$=377.9

CAS — 3736-08-1 (fenetylline); 1892-80-4 (fenetylline hydrochloride).
ATC — N06BA10.
ATC Vet — QN06BA10.
UNII — YA7K8ADZ2V.

Profile

Fenetylline is a theophylline derivative of amfetamine with properties similar to those of dexamfetamine (p. 2319.1). It is given orally in the management of narcolepsy (p. 2314.3) in an initial dose of 25 mg daily, increased to usual maintenance doses of 50 to 100 mg daily in 2 divided doses; no more than 150 mg daily should be used. It has also been used in the management of hyperactivity disorders. Fenetylline is subject to abuse.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Captagon†.

Fenfluramine Hydrochloride

(BANM, USAN, rINNM) ⊗

AHR-3002; Fenfluramina, hidrocloruro de; Fenfluramine, Chlorhydrate de; Fenfluramini Hydrochloridum; Hidrocloruro de fenfluramina; S-768; Фенфлюрамина Гидрохлорид.

N-Ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride.

$C_{12}H_{16}F_3N,HCl$=267.7

CAS — 458-24-2 (fenfluramine); 404-82-0 (fenfluramine hydrochloride).
ATC — A08AA02.
ATC Vet — QA08AA02.
UNII — 3KC089243P.

Uses and Administration

Fenfluramine is an indirect-acting sympathomimetic related to amfetamine, but at standard doses it usually depresses rather than stimulates the CNS. It appears to stimulate the release of serotonin and selectively inhibits its reuptake resulting in increased CNS serotonin concentrations. It may also increase glucose utilisation and lower blood-glucose concentrations.

Fenfluramine was formerly given orally as the hydrochloride in the treatment of obesity but was generally withdrawn worldwide after reports of valvular heart defects.

Adverse Effects and Precautions

As for Dexamfetamine, p. 2319.2, but fenfluramine usually depresses rather than stimulates the CNS. Fenfluramine has been associated with serious cardiovascular toxicity. Pulmonary hypertension led to certain precautions being imposed upon its use and subsequent reports of valvular heart defects led to its general withdrawal worldwide.

Effects on the cardiovascular system. The association of primary *pulmonary hypertension* with the use of anorectics including fenfluramine, dexfenfluramine, and phentermine is well recognised.[1-3] Both reversible and irreversible cases have been reported and in some cases it has proved fatal.[1,4-9] The condition appears to be linked to prolonged or repeated therapy.[1,10] In 1992 the UK CSM advised that treatment should not exceed 3 months[1] but later in 1997 it revised its recommendations for fenfluramine and dexfenfluramine allowing treatment for up to 12 months under certain conditions.[2] The CSM stated that treatment could be continued beyond 3 months only if there had been a satisfactory response (more than 10% weight loss) and that this loss was maintained. Patients should also be monitored for symptoms of pulmonary hypertension. For other anorectics such as phentermine the maximum duration of treatment remained 3 months.

However, shortly after this, a report was published[11] that outlined an association between the use of a fenfluramine-phentermine combination and the development of *valvular heart disease* in 24 patients. Initially, the response by the CSM was to advise against the use of combinations of anorectics[12] although subsequently fenfluramine, along with dexfenfluramine, was withdrawn from the world market after more cases became known.[13,14] By September 1997 the FDA in the USA[14] had received 144 reports of valvulopathy, including the original 24, associated with fenfluramine or dexfenfluramine, with or without phentermine; none were associated with phentermine treatment alone. As a consequence the US authorities made recommendations[14] for the screening of all patients who had previously received fenfluramine or dexfenfluramine in order to detect heart valve lesions and to provide optimal care. Further studies[15-21] have supported the association with valvular abnormalities, and suggested that prolonged exposure or exposure to high doses of dexfenfluramine or fenfluramine increased the risk; clinically important disease would probably not develop in most patients with only short-term exposure.[22]

In 2000, the European Commission called for the withdrawal of all anorectics from the European market. Those anorectics involved in the decision included clobenzorex, diethylpropion, fenproporex, mazindol, mefenorex, phendimetrazine, phenmetrazine, and phentermine. However in 2002, after an appeal by some manufacturers, the European Court ruled that the Commission did not have the authority to withdraw marketing authorisations.

Subsequently, some anorectics have been allowed back onto the European market.

1. CSM. Fenfluramine (Ponderax Pacaps), dexfenfluramine (Adifax) and pulmonary hypertension. *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
2. CSM/MCA. Anorectic agents: risks and benefits. *Current Problems* 1997; 23: 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
3. Abenhaim L, *et al.* Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996; 335: 609–16.
4. Douglas JG, *et al.* Pulmonary hypertension and fenfluramine. *BMJ* 1981; 283: 881–3.
5. McMurray J, *et al.* Irreversible pulmonary hypertension after treatment with fenfluramine. *BMJ* 1986; 292: 239–40.
6. Fotiadis I, *et al.* Fenfluramine-induced irreversible pulmonary hypertension. *Postgrad Med J* 1991; 67: 776–7.
7. Atanassoff PG, *et al.* Pulmonary hypertension and dexfenfluramine. *Lancet* 1992; 339: 436.
8. Cacoub P, *et al.* Pulmonary hypertension and dexfenfluramine. *Eur J Clin Pharmacol* 1995; 48: 81–3.
9. Roche N, *et al.* Pulmonary hypertension and dexfenfluramine. *Lancet* 1992; 339: 436–7.
10. Thomas SHL, *et al.* Appetite suppressants and primary pulmonary hypertension in the United Kingdom. *Br Heart J* 1995; 74: 600–63.
11. Connolly HM, *et al.* Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; 337: 581–8. Correction. *ibid.*: 1783.
12. CSM/MCA. Anorectic agents and valvular heart disease. *Current Problems* 1997; 23: 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 23/05/06)
13. CSM/MCA. Fenfluramine and dexfenfluramine withdrawn. *Current Problems* 1997; 23: 13–14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023238&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
14. Anonymous. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: US Department of Health and Human Services interim public health recommendations, November 1997. *MMWR 1997*; 46: 1061–6.
15. Khan MA, *et al.* The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med* 1998; 339: 713–18.
16. Jick H, *et al.* A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. *N Engl J Med* 1998; 339: 719–24.
17. Weissman NJ, *et al.* An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. *N Engl J Med* 1998; 339: 725–32.
18. Gardin JM, *et al.* Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. *JAMA* 2000; 283: 1703–9.
19. Lepor NE, *et al.* Dose and duration of fenfluramine-phentermine therapy impacts the risk of significant valvular heart disease. *Am J Cardiol* 2000; 86: 107–10.
20. Jollis JG, *et al.* Fenfluramine and phentermine and cardiovascular findings: effect of treatment duration on prevalence of valve abnormalities. *Circulation* 2000; 101: 2071–7.
21. Dahl CF, *et al.* Valvular regurgitation and surgery associated with fenfluramine use: an analysis of 5743 individuals. *BMC Med* 2008; 6: 34. Available at: http://www.biomedcentral.com/content/pdf/1741-7015-6-34.pdf (accessed 23/06/09)
22. Devereux RB. Appetite suppressants and valvular heart disease. *N Engl J Med* 1998; 339: 765–6.

Effects on the liver. The UK MHRA had warned[1] that there had been cases of hepatotoxicity associated with adulteration of traditional Chinese slimming medicines with fenfluramine and/or nitrosofenfluramine. Nitrosofenfluramine was known to be hepatotoxic.

1. MHRA. Shubao slimming capsules containing fenfluramine and nitrosofenfluramine (issued 28th April, 2004). Available at: http://www.mhra.gov.uk/home/groups/es-herbal/documents/websiteresources/con009291.pdf (accessed 11/08/08)

Fenproporex Hydrochloride *(rINNM)* ⊗

N-2-Cyanoethylamphetamine Hydrochloride; Fenproporex, Chlorhydrate de; Fenproporex, hidrocloruro de; Fenproporexi Hydrochloridum; Hidrocloruro de fenproporex; Фенпропорекса Гидрохлорид.

(±)-3-(α-Methylphenethylamino)propionitrile hydrochloride.

$C_{12}H_{16}N_2HCl$=224.7

CAS — 15686-61-0 (fenproporex); 18305-29-8 (fenproporex hydrochloride).

UNII — 09PE91J6V6.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of fenproporex:

Pasexes.

Profile

Fenproporex is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.1). After oral doses it is reported to be metabolised to amfetamine. Fenproporex has been given as the hydrochloride, the diphenylacetate, and as a resinate.

Fenproporex hydrochloride has been used as an anorectic in the treatment of obesity although the use of stimulants in this way is no longer recommended. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Desobesi-M; *Chile*: Salcal; *Mex.*: Feprorex; Ifa-Diety.

Multi-ingredient Preparations. *Arg.*: Tratobes; *Mex.*: Esbelcaps.

Lisdexamfetamine Mesilate *(rINNM)* ⊗

Lisdexamfetamine Dimesylate (USAN); Lisdexamfétamine, Mésilate de; Lisdexamfetamini Mesilas; Mesilato de lisdexanfetamina; NRP-104; Лисдексамфетамина Мезилат.

(2*S*)-2,6-Diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate.

$C_{15}H_{25}N_3O.(CH_4O_3S)_2$=455.6

CAS — 608137-32-2 (lisdexamfetamine); 608137-33-3 (lisdexamfetamine mesilate).

ATC — N06BA12.

ATC Vet — QN06BA12.

UNII — SJT761GEGS.

Profile

Lisdexamfetamine is a prodrug of dexamfetamine (p. 2319.1). It is used as a central stimulant in the treatment of attention deficit hyperactivity disorders (see Hyperactivity, p. 2314.1).

Lisdexamfetamine is given orally as the mesilate and doses are expressed in terms of this salt. For adults and children aged 6 years and over, the starting dose is 30 mg once daily in the morning, increased if necessary in increments of 10 or 20 mg daily at about weekly intervals, up to a total maximum dose of 70 mg daily. It may also be used for maintenance treatment in adults. In patients taking lisdexamfetamine for extended periods, the need for continued treatment should be assessed periodically and, where possible, interrupted occasionally.

References.

1. Blick SK, Keating GM. Lisdexamfetamine. *Paediatr Drugs* 2007; 9: 129–35.
2. Cowies BJ. Lisdexamfetamine for treatment of attention-deficit/hyperactivity disorder. *Ann Pharmacother* 2009; 43: 669–76.
3. Weber J, Siddiqui MAA. Lisdexamfetamine dimesylate: in attention-deficit hyperactivity disorder in adults. *CNS Drugs* 2009; 23: 419–25.
4. Popovic B, *et al.* Lisdexamfetamine: a prodrug for the treatment of attention-deficit/hyperactivity disorder. *Am J Health-Syst Pharm* 2009; 66: 2005–12.
5. Findling RL, *et al.* Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2011; 50: 395–405.
6. Childress AC, Sallee FR. The use of lisdexamfetamine dimesylate for the treatment of ADHD. *Expert Rev Neurother* 2012; 12: 13–26.

Administration in children. For doses of lisdexamfetamine mesilate in children and adolescents, see above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Venvanse; *Canad.*: Vyvanse; *UK*: Elvanse; *USA*: Vyvanse.

Lobelia ⊗

Indian Tobacco; Tabaco Indio; Лобелия Одутлая (*Lobelia inflata*).

ATC Herb — HR03WA5002 (Lobelia inflata: herb).

UNII — 1G4GK01F67.

Description. Lobelia consists of the dried aerial parts of *Lobelia inflata* (Lobeliaceae). Lobeline is the main alkaloidal constituent.

Lobeline Hydrochloride *(BANM, rINNM)* ⊗

Alpha-lobeline Hydrochloride; Hidrocloruro de lobelina; Lobeliinihydrokloridi; Lobelina, hidrocloruro de; Lobéline, chlorhydrate de; Lobelin-hidroklorid; Lobelinhydrochlorid; Lobelin-hydrochlorid; Lobelinhydroklorid; Lobelini Hydrochloridum; Lobelino hidrochloridas; Лобелина Гидрохлорид.

2-[6-(β-Hydroxyphenethyl)-1-methyl-2-piperidyl]acetophenone hydrochloride.

$C_{22}H_{27}NO_2HCl$=373.9

CAS — 90-69-7 (lobeline); 134-63-4 (lobeline hydrochloride).

UNII — 963834CB88.

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

Ph. Eur. 8: (Lobeline Hydrochloride). A white or almost white microcrystalline powder. Sparingly soluble in water; freely soluble in alcohol; soluble in dichloromethane. A 1% solution in water has a pH of 4.6 to 6.4. Protect from light.

Lobeline Sulfate *(BANM, rINNM)* ⊗

Lobelina, sulfato de; Lobéline, Sulfate de; Lobeline Sulphate; Lobelini Sulfas; Sulfato de lobelina; Лобелина Сульфат.

$(C_{22}H_{27}NO_2)_2H_2SO_4$=773.0

CAS — 134-64-5.

UNII — 4CJ480V2HP.

Uses and Administration

Lobelia is the dried aerial parts of *Lobelia inflata* (Lobeliaceae). Lobeline is the main alkaloidal constituent and has peripheral and central effects similar to those of nicotine (p. 2569.3).

Lobelia has been used mainly in preparations aimed at relieving respiratory-tract disorders. Lobeline has been given orally as the hydrochloride or sulfate as a smoking deterrent. Lobelia has been used similarly given either orally or incorporated into herbal cigarettes.

Smoking cessation. Reviews of smoking cessation therapy (p. 2570.2) generally consider lobeline to have little benefit compared with placebo.[1-3]

1. Nunn-Thompson CL, Simon PA. Pharmacotherapy for smoking cessation. *Clin Pharm* 1989; 8: 710–20.
2. Gourlay SG, McNeil JJ. Antismoking products. *Med J Aust* 1990; 153: 699–707.
3. Stead LF, Hughes JR. Lobeline for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1997 (accessed 16/05/05).

Adverse Effects

Adverse effects of lobelia and lobeline include nausea and vomiting, coughing, tremor, and dizziness. Symptoms of overdosage include profuse diaphoresis, paresis, tachycardia, hypothermia, hypotension, and coma; fatalities have occurred.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Burt it Out; *Spain*: Smokeless†; *UK*: Lobelina.

Multi-ingredient Preparations. *Braz.*: Bronquidex; Brontoss; MM Expectorante; *Canad.*: Calmane; *Chile*: Paltomiel Plus; Pulmagol; Ramistos; *Spain*: Pazbronquial; *UK*: Antibron; Asthma & Catarrh Relief; Balm of Gilead†; Chest Mixture; Herbelix; Horehound and Aniseed Cough Mixture; Modern Herbals Cold & Congestion; Quitacoff; Vegetable Cough Remover; *Venez.*: Novacodin.

Homoeopathic Preparations. *Austria*: Bronchalis-Heel; Lobelia Med Complex; Luffa compositum-Heel; Tartephedreel; *Canad.*: Breathe More; Bronkeel†; Homeo-Form T†; Nixotinex; *Chile*: Drosemiel; Similibus; TBR/X; *Cz.*: Bronchalis-Heel; Luffeel; *Fr.*: Boripharm No 12†; Boripharm No 3; Drosera Complexe No 64; Gentiana Complexe No 33†; Lobelia Complexe No 74†; Santaherba; *Ger.*: Angioton H; Angioton S†; Antinicoticum mono†; Aralis; Asthmavowen-N†; Broncho-Injektopas; Bronchopas; Corselect N; HanoTussan; Lobelia comp; Luffeel Comp; Neolin-Entoxin; Presselin All; Pulmo Bronchialcomplex; Pulmo-cyl Ho-Len-Complex; Roth's RKT Tropfen; Tabarell; *Hung.*: Bronchalis-Heel; Luffeel; *Neth.*: Bronchalis; Lergilite; Luffeel H; *Rus.*: Sambucus-Plus (Самбухус-Плюс); Tabacum-Plus (Табакум-Плюс); *Switz.*: Bronchalis-Heel; Regenaplex Nr. 24b.

Lorcaserin *(rINN)*

Lorcaserina; Lorcasérine; Lorcaserinum; Лоркасерин.

(1*R*)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

$C_{11}H_{14}ClN$=195.7

CAS — 616202-92-7.

UNII — 637E494O0Z.

Lorcaserin Hydrochloride *(USAN, rINNM)*

APD-356; Hidrocloruro de lorcaserina; Lorcasérine, Chlorhydrate de; Lorcaserini Hydrochloridum; Лоркасерин а Гидрохлорид.

$C_{11}H_{14}ClN.HCl$=232.1

CAS — 846589-98-8.

UNII — 0QJF08GDPE.

Uses and Administration

Lorcaserin, a selective serotonin agonist that acts at 5-HT_{2C} receptors, is used in the management of obesity (p. 2315.1). It may also be used in overweight patients (BMI of 27 kg/m² or more) if other risk factors such as hypertension, diabetes mellitus, or hyperlipidaemias are present.

Lorcaserin hydrochloride is given orally in a usual dose of 10 mg twice daily. Treatment should be stopped if the patient has not lost at least 5% of initial body-weight by week 12 of starting therapy; continued treatment is unlikely to be of benefit.

References.
1. Smith SR, *et al.* APD356-004 Study Group. Lorcaserin (APD356), a selective 5-HT_{2C} agonist, reduces body weight in obese men and women. *Obesity (Silver Spring)* 2009; 17: 494 503.
2. Smith SR, *et al.* Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010; 363: 245–56.
3. Bai B, Wang Y. The use of lorcaserin in the management of obesity: a critical appraisal. *Drug Des Devel Ther* 2010; 5: 1 7.
4. Redman LM, Ravussin E. Lorcaserin for the treatment of obesity. *Drugs Today* 2010; 46: 901–10.
5. Fidler MC, *et al.* BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab* 2011; 96: 3067 77.
6. Hurren KM, Berlie HD. Lorcaserin: an investigational serotonin 2C agonist for weight loss. *Am J Health-Syst Pharm* 2011; 68: 2029–37.
7. O'Neil PM, *et al.* Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012; 20: 1426–36.

Adverse Effects and Precautions

The most common adverse effects reported with the use of lorcaserin in non-diabetic patients are headache, dizziness, fatigue, nausea, dry mouth, and constipation; hypoglycaemia, headache, back pain, cough, and fatigue occur commonly in diabetic patients. Other adverse effects in all patients include euphoria, depression and suicidal ideation, and eye disorders. Patients should be monitored for emergence or worsening of depression and/or suicidal ideation, and changes in mood or behaviour; lorcaserin should be stopped in those who develop suicidal thoughts or behaviours. Laboratory abnormalities such as lowered haemoglobin, lymphocyte, and neutrophil count, and hyperprolactinaemia have been reported; periodic monitoring of complete blood count should be considered during lorcaserin therapy. Bradycardia and symptoms suggestive of a serotonin syndrome have also occurred. Lorcaserin should be used with caution in patients with bradycardia or a history of heart block greater than first degree. Valvular heart disease has been associated with some serotonergic drugs (see Effects on the Cardiovascular System under Fenfluramine, p. 2322.3); lorcaserin may need to be stopped in those who develop signs and symptoms of cardiac valvulopathy or a new murmur. Because priapism is a potential effect of 5-HT_{2C} receptor agonism, lorcaserin should be used with caution in men with conditions predisposing to such an event.

Lorcaserin should be used with caution in patients with moderate renal or severe hepatic impairment; use is not recommended in those with severe renal impairment or end-stage renal disease.

Lorcaserin may impair cognitive function; if affected, patients should not drive or operate machinery.

Interactions

Lorcaserin should not be used with serotonergic or dopaminergic drugs that are potent 5-HT_{2B} agonists and known to increase the risk of cardiac valvulopathy, such as cabergoline. It should be used with extreme caution with other drugs known to act on the serotonergic neurotransmitter system, such as bupropion, dextromethorphan, lithium, MAOIs, SSRIs, tramadol, tricyclic antidepressants, triptans, and St John's wort, because of the increased risk of serotonin syndrome. Lorcaserin inhibits cytochrome P450 isoenzyme CYP2D6-mediated metabolism and should be used with caution with drugs that are substrates of this isoenzyme.

Weight loss may increase the risk of hypoglycaemia in patients with type 2 diabetes mellitus who are using insulin and/or oral antidiabetics; the dosage of antidiabetics may need to be decreased.

Pharmacokinetics

Lorcaserin is absorbed from the gastrointestinal tract and peak plasma concentrations occur after 1.5 to 2 hours. It has a plasma half-life of about 11 hours and is distributed into the CSF and CNS. It is moderately (about 70%) bound to plasma proteins. Lorcaserin is extensively metabolised in the liver by multiple enzymatic pathways to principally inactive metabolites. Excretion is mainly in the urine with about 2% recovered in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA:* Belviq.

Mazindol *(BAN, USAN, rINN)* ⊗

42-548; AN-448; Matsindoli; Mazindolum; SaH-42548; Мазиндол.

5-(4-Chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol.

$C_{16}H_{13}ClN_2O$=284.7

CAS — 22232-71-9.

ATC — A08AA05.

ATC Vet — QA08AA05.

UNII — C56709M5NH.

Pharmacopoeias. In *US.*

USP 36: (Mazindol). A white to off-white crystalline powder, having not more than a faint odour. Insoluble in water; slightly soluble in chloroform and in methyl alcohol. Store in airtight containers.

Profile

Mazindol is a central stimulant with actions similar to those of dexamfetamine (p. 2319.1), although structurally the two compounds are unrelated. It appears to inhibit reuptake of dopamine and noradrenaline. It has been used as an anorectic, given orally in the treatment of obesity, although stimulants are no longer recommended for this indication. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Mazindol has been investigated in the treatment of Duchenne muscular dystrophy.

Adverse effects. Testicular pain developed in 8 men after taking mazindol.[1]

1. McEwen J, Meyboom RHB. Testicular pain caused by mazindol. *BMJ* 1983; 287: 1763–4.

Interactions. For a report of mazindol interacting with *lithium* to cause lithium toxicity, see Central Stimulants, p. 432.1.

Narcolepsy. Mazindol has been reported[1-4] to be beneficial in patients with narcolepsy and associated cataplexy (p. 2314.3). A wide range of doses has been used: 3 to 8 mg daily in one study,[1] 1 mg weekly to 16 mg daily in another;[3] children have been given 1 to 2 mg daily.[4]

1. Parkes JD, Schachter M. Mazindol in the treatment of narcolepsy. *Acta Neurol Scand* 1979; 60: 250–4.
2. Shindler J, *et al.* Amphetamine, mazindol, and fencamfamin in narcolepsy. *BMJ* 1985; 290: 1167–70.
3. Alvarez B, *et al.* Mazindol in long-term treatment of narcolepsy. *Lancet* 1991; 337: 1293–4.
4. Allsopp MR, Zaiwalla Z. Narcolepsy. *Arch Dis Child* 1992; 67: 302–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Afilan; Dimagrit; Fagolip Plus; Samonter†; *Braz.*: Absten S†; Fagolipo; Moderine; *China*: Mei Xin Da (美新达); *Gr.*: Teronac; *Hong Kong*: Qualizindol; *Indon.*: Teronac; *Jpn*: Sanorex; *Mex.*: Diestet; Ila Lose†; Ilezol; MZ1; Obendol; Rezin; Solucaps; *Philipp.*: Mazzol; *Singapore*: Teronac†.

Multi-ingredient Preparations. *Arg.*: Maxitratobest†.

Pharmacopoeial Preparations
USP 36: Mazindol Tablets.

Metamfetamine Hydrochloride *(rINNM)* ⊗

d-Deoxyephedrine Hydrochloride; *d*-Desoxyephedrine Hydrochloride; Hidrocloruro de metanfetamina; Métamfétamine, Chlorhydrate de; Metamfetamini Hydrochloridum; Metanfetamina, hidrocloruro de; Methamphetamine Hydrochloride; Methamphetamini Hydrochloridum; Methylamphetamine Hydrochloride; Phenylmethylaminopropane Hydrochloride; Метамфетамина Гидрохлорид.

(+)-*N*,α-Dimethylphenethylamine hydrochloride.

$C_{10}H_{15}N.HCl$=185.7

CAS — 537-46-2 (metamfetamine); 51-57-0 (metamfetamine hydrochloride).

ATC — N06BA03.

ATC Vet — QN06BA03.

UNII — 997F43Z9CV.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of metamfetamine:

20/20; 222; 417; Agua; Albino Poo; Alffy; All tweakend long; Amp; Anny; Anything going on; Artie; Bache knock; Bache rock; Bag chasers; Baggers; Barney dope; Batak; Bathtub crank; Bato; Batu; Batu kilat; Batunas; Batuwhore; Beannies; Beegokes; Bianca; Bikerdope; Billy; Bitch; Biznack; Black; Black beauty; Blade; Blanco; Bling; Blizzard; Blue acid; Blue belly; Blue devils; Blue funk; Blue meth; Bomb; Bombita; Bombitas; Boo; Booger; Boorit-Cebuano; Bottles; Boo-Yah!; Brian Ed; Brown; Buff stick; Bugger sugar; Buggs; Bump; Bumps; Buzzard dust; Caca; Cale Gerst; California white cross; Candy; Cankinstien; Cartwheels; CC; ChaChaCha; Chach; Chalk; Chalk dust; Champagne; Chank; Cheebah; Cheese; Chicken; Chicken feed; Chicken flippin; Chikin; Chimichanga; Chingadera; Chittle; Chizel; Chiznad; Choad; Chris; Chrissy; Christal; Christina; Christine; Christmas tree; Christy; Chunkylove; Cinnamon; Clavo; Clean out the chimney; Clear; Coco; Coffee; Colorado Rockies; Cookies; Cotton Candy; CR; Crack Whore; Crank; Cranster Gansters; Creek Rock; Cri, cri; Criddle; Criddy; Cringe; Crink; Crip; Cris; Crisco; Crissie; Crissy; Cristina; Cristy; Critty; Crizzy; Croak; Crossles; Crothch dope; Crow; Crunk; Crypto; Crysnax; Crystal; Crystal glass; Crystal meth; Crystal methadrine; Crystalight; Crystals; Cube; D; Debbie; Desocsins; Desogtion; Devil dust; Devils dandruff; Devils drug; Dingles; Dirt; Dirty; Dizzle; Dizzo; Dizzy D; D-Monic; Do da; Doe; Doody; Doo-my-lau; Dope; Drano; Dummy dust; Dunk; Dyno; El Gato Diablo; Epimethrine; Epod; Eraser dust; Ethyl-M; Evil yellow; Fast; Fatch; Fedrin; Fil-layed; Fire; Fizz whizz; Fizz Wizz; Flash; Fluff; Future; G; G-unit; Gackle-a Fackle-a; Gab; Gagger; Gak; Gas; Gear; Geek; Geep; Geeter; Gemini; George; Get geared up; Getgo; Gina; Glass; Go; Go-ey; Go Past; Go-fast; Go-go; Go-go juice; Gonzales; Goop; Go Pills; Goose-Egg; Got anything; Grads; Granulated orange; Grit; Gumption; Gyp; Haiwaiian salt; Hank; Hanyak; Hard Crystal; Hawaiis finest; Hidi; High Riders; High speed chicken feed; Highthen; Hillbilly crack; Hippy crack; Hironpon; Hiropon; Holy Smoke; Homework; Honk the BoBo; Hoo; Horse mumpy; Hot Ice; Hydro; Hypes; "I want to talk to Gina tonight"; Ibski; Ice; Ice cream; Icee; Ink; Ish; Izice; Jab; Jasmine; Jenny Crank; Jenny Crank Program; Jet fuel; Jetfuel; Jib; Jib nugget; Jibb Tech Warrier; Jibber jabbin; Jinga; Juddha; Juice; Junk; Kaksonjae; Kibble; Killer; KooLAID; Kryptonite; L.A.; LA Glass; L.A. glass; la glass; L.A. ice; LA Ice; Lamer; Laundry detergent; Leapers; Lemon drop; Life; Lily; Linda; Linga; Livin the Dream; Load of Laundry; Lost weekend; Love; Low; Lucille; M man; Magic; Maui-wowie; Met; Meth; Meth amps; Meth monsters; Methaine; Methandfriend; Methandfriendsofmine; Methanfelony; Methatrim; Methedrine; Methlies Quik; Methmood; Method; Mexican crack; Minibennies; Monster; Moon Juice; Motivation; Motivation in a bag; Motorcycle crack; Moving on G; Nazi crank; Nazi dope; Nazi vitamens; Nazimeth; Ned; Newday; Night Train; No doze; Nose candy; On a good one; Orange; OZs; P; Patsie; Peaking; Peanut butter; Peel dope; Pervatine; Pervitin; Phazers; Phets; Philopon; Pieta; Piko; Pink; Pink elephants; Pink hearts; Poison; Poof; Pookie; Poop; Poop'd out; Poor man's coccaine; Poor man's coke; Poot; Pootananny; Poppers; Powder; Powder monkeys; Powder point; Project propellant; Puddle; Pump; Pure; Q'd; Quarter Tee Bag; Quartz; Quick; Quill; Rachet jaw; Rails; Rank; Red; Red devils; Red phosphorus; Redneck cocaine; Redneck heroin; Richie Rich; Rip; Rippers; Robin eggs; Rock; Rock crank; Rocket fuel; Rocky mountain high; Rosebud; Rudy; Rudy's; Rumdumb; Running Pizo; Sack; Sam's sniff; Sarahs; Satan dust; Scante; Scap; Schlep rock; Schmiz; Sciznac; Scooby snax; Scootie; Scud; Scwadge; Sean; Sha-bang; Shab; Shabs; Shabu; Shamers; Shards; Shia; Shit; Shiznac; Shiznack; Shiznastica; Shiznit; Shiznittlebang; Shiznitty; Shizzo; Shnizzie snort; Shwack; Skeech; Sketch; Ski; Skitz; Sky rocks; Sliggers; Smiley smile; Smurf dope; Smzl; Snaps; Sniff; Snow; Soap; Soap dope; Space food; Spaceman; Spackle; Spagack; Sparacked; Sparked; Sparkle; Speckled birds; Speed; Speed racer; Spin, spin, spin; Spinack; Spindarella; Spinney Boo; Spinning; Spishak; Splash; Spook; Spoosh; Sprack; Sprizzlefracked; Sprung; Spun Ducky Woo; Squawk; Stallar; Sto-Pid; Stove top; Styels; Sugar; Suger; Super ice; Sweetness; Swerve; Syabu; Ta'doww; Talkie; Tanner; Tasmanian Devil; T.D.; Teena; Tenner; Terry; Texas Tea; The attenborough; The New Prozac; The White House; Tic Tical; Tick tick; Tik; Time; Tina; Tink Dust; Tish; Tobats; Tootie; Toots; Torqued; Trash; Trippin Trip; Truck Stop Special; Tubbytoast; Tuk; Tuk-tuk; Tutu; Twack; Twacked out; Tweak; Tweedle Doo; Tweek; Tweezwasabi; Twistaflexin; Twiz; Twizacked; Ugly Dust; Upside-down b; Uppers; Vanilla Pheromones; Wake; Wash; Water; Way; We We We; Wet; Whacked; Whip; White; White bitch; White Cross; White Crosses; White Crunch; White ink; White junk; White lady; White pony; Whiz; Whizz; Who-Ha; Wigg; Work; Working man's cocaine; Xaing; YAMA; Ya Ba; Yaaba; Yaba; Yammer Bammer; Yank; Yankee; Yay; Yead Out; Yellow bam; Yellow barn; Yellow jackets; Yellow powder; Zingin; Zip; Zoiks; Zoom.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Methamphetamine Hydrochloride). White, odourless or practically odourless, crystals or crystalline powder. Freely soluble in water, in alcohol, and in chloroform; very slightly soluble in ether. Its solutions in water have a pH of about 6. Store in airtight containers. Protect from light.

Uses and Administration

Metamfetamine hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions and uses similar to those of dexamfetamine (p. 2319.2).

It has been given orally in the treatment of attention deficit hyperactivity disorder (see Hyperactivity, p. 2314.1) in children aged 6 years and over, although it is not one of

the main stimulants used. Initial doses are 5 mg once or twice daily, increased if necessary by 5 mg at weekly intervals to the optimum effective dose, usually 20 to 25 mg daily given in 2 divided doses.

Metamfetamine hydrochloride has also been used as an anorectic in the management of obesity (p. 2315.1), although amfetamines are no longer recommended for this indication. A dose of 5 mg before each meal has been given orally. Treatment should be for no longer than a few weeks.

Metamfetamine hydrochloride has also been used parenterally as a pressor agent.

The laevorotatory form, levmetamfetamine (p. 1668.3) is used as a nasal decongestant.

Administration in children. For doses of metamfetamine hydrochloride in children and adolescents, see Uses and Administration, p. 2324.3.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2.

Metamfetamine is subject to extensive abuse.

Abuse. Pulmonary oedema,[1,2] cardiomyopathy,[2,3] and choreoathetosis and rhabdomyolysis[4] have occurred after smoking of metamfetamine crystals. It is also abused orally and intravenously, and has been associated with fatalities;[5] rectal abuse has been reported.[6,7] Dental problems such as rampant caries and tooth wear and fracture, colloquially termed "meth mouth", may occur with long-term abuse.[8,9] A marked increase in prevalence of abuse in recent years, particularly in the USA, has led to increased research into the consequences of such abuse and methods for management.[10-13]

A study of former users suggests that metamfetamine abuse may cause long-term neuronal damage.[14]

There has been concern about metamfetamine abuse during pregnancy, suggesting its use has been associated with fetal growth restriction.[15]

1. Nestor TA, *et al.* Acute pulmonary oedema caused by crystalline methamphetamine. *Lancet* 1989; **ii**: 1277–8.
2. Hong R, *et al.* Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA* 1991; **265**: 1152–4.
3. Yeo K-K, *et al.* The association of methamphetamine use and cardiomyopathy in young patients. *Am J Med* 2007; **120**: 165–71.
4. Sperling LS, Horowitz JL. Methamphetamine-induced choreosthetosis and rhabdomyolysis. *Ann Intern Med* 1994; **121**: 986.
5. Albertson TE, *et al.* Methamphetamine and the expanding complications of amphetamines. *West J Med* 1999; **170**: 214–19.
6. Cantrell FL, *et al.* Transrectal methamphetamine use: a novel route of exposure. *Ann Intern Med* 2006; **145**: 78–9.
7. Gupta M, *et al.* Bottoms up: methamphetamine toxicity from an unusual route. *Western J Emerg Med* 2009; **10**: 58–60.
8. Curtis EK. Meth mouth: a review of methamphetamine abuse and its oral manifestations. *Gen Dent* 2006; **54**: 125–9.
9. Donaldson M, Goodchild JH. Oral health of the methamphetamine abuser. *Am J Health-Syst Pharm* 2006; **63**: 2078–82. Correction. *ibid.*: 2180.
10. Cho AK, Melega WP. Patterns of methamphetamine abuse and their consequences. *J Addict Dis* 2002; **21**: 21–34.
11. Rawson RA, *et al.* Treatment of methamphetamine use disorders: an update. *J Subst Abuse Treat* 2002; **23**: 145–50.
12. Cretzmeyer M, *et al.* Treatment of methamphetamine abuse: research findings and clinical directions. *J Subst Abuse Treat* 2003; **24**: 267–77.
13. Lineberry TW, Bostwick JM. Methamphetamine abuse: a perfect storm of complications. *Mayo Clin Proc* 2006; **81**: 77–84.
14. Ernst T, *et al.* Evidence for long-term neurotoxicity associated with methamphetamine abuse: a ^{1}H MRS study. *Neurology* 2000; **54**: 1344–9.
15. Smith LM, *et al.* The infant development, environment, and lifestyle study: effects of prenatal methamphetamine exposure, polydrug exposure, and poverty on intrauterine growth. *Pediatrics* 2006; **118**: 1149–56.

Interactions

As for Dexamfetamine Sulfate, p. 2320.2.

Pharmacokinetics

Like most amfetamines (see Dexamfetamine Sulfate, p. 2320.2) metamfetamine is readily absorbed from the gastrointestinal tract and is distributed into most body tissues. It is partially metabolised in the liver and excreted in the urine.

References.
1. Shappell SA, *et al.* Chronopharmacokinetics and chronopharmacodynamics of dextromethamphetamine in man. *J Clin Pharmacol* 1996; **36**: 1051–63.
2. Harris DS, *et al.* The bioavailability of intranasal and smoked methamphetamine. *Clin Pharmacol Ther* 2003; **74**: 475–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Cidrin†; *USA*: Desoxyn.

Pharmacopoeial Preparations

USP 36: Methamphetamine Hydrochloride Tablets.

Methcathinone ⊗

Ephedrone; Methylcathinone; Monomethylpropion; Меткатинон.

2-(Methylamino)-1-phenyl-1-propan-1-one.

$C_{10}H_{13}NO$=163.2

CAS — 5650-44-2

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methcathinone:

Bathtub speed; Cadillac express; Cat; Catt; Cosmos; Crank; Gagers; Gaggers; Go fast; Go-fast; Goob; Jee cocktail; Jeff; Khat; Mulk; Mulka; Qat; Slick superspeed; Sniff; Somali; Somali tea; Speed; Star; Stat; The C; Tweak; Tweek; Tweeker; Wild cat; Wonder star.

4-Methylmethcathinone ⊗

Mephedrone; 4-MMC.

$C_{11}H_{15}NO$=177.2

CAS — 1189805-46-6.

UNII — 8BA8T27317.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of 4-Methylmethcathinone:

Bubble; Bubbleluv; Bubbles; Drone; M kat; MCAT; M-Cat; MD3; Meow; Meow-meow; Meph; Methadrone; Miaow; Miaow miaow; MMCAT; Moonshine; Neo drones; Plant feeder; Roxy; Rush; SC spirit; Sub coca I; Top cat; White magic.

Profile

Methcathinone, a methyl derivative of cathinone (p. 2318.2), produces CNS stimulant effects similar to those of the amfetamines (see Dexamfetamine, p. 2319.1) and is subject to abuse. The methyl derivative 4-methylmethcathinone (mephedrone; 4-MMC) is also subject to abuse. (See also Abuse, under Catha, p. 2318.3).

References.
1. Belhadj-Tahar H, Sadeg N. Methcathinone: a new postindustrial drug. *Forensic Sci Int* 2005; **153**: 99–101.

Methylenedioxymethamfetamine ⊗

MDMA; 3,4-Methylenedioxymethamphetamine; Methylenedioxymethamphetamine; Metilendioximetanfetamina.

N,α-Dimethyl-1,3-benzodioxole-5-ethanamine.

$C_{11}H_{15}NO_2$=193.2

CAS — 42542-10-9.

UNII — KETSEN21RM.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methylenedioxymethamfetamine:

007s; 69s; Acid; Adam; Adam MTX; AKA; Anastasia; Apples; Baby slits; Bacalao; Bart Simpson; Batmans; B-bombs; Bean; Beans; Bens; Benzedrine; Bermuda triangles; Bibs; Bicho; Bickies; Bikkies; Biphetamine; Biscuits; Blue kisses; Blue lips; Blue nile; Booty juice; Bomber; Brownies; Burgers; Candies; Candy; Care bears; Cat in the hats; Charity; Chocolate chips; Chrystal methadrine; Clarity; Cloud nine; Clovers; Cowies; Cristal; Crowns; Crystal; Dancing Shoes; Dead road; Debs; Decadence; Deccadence; Denis the Menace; Dennis the Menaces; Dex; Dexedrine; Diamonds; Diamond Whites; Disco biscuit; Disco biscuits; Doctor; Dollars; Dolls; Dolphins; Doobies; Dove; Doves; Drivers; E; EA1475; Eazy; Eazy E; E-ball; Ebeneezer; E-bomb; E-bombs; Eccies; Ecsta; Ecstacy; Ecstasy; Ecstasy Tablets; Eddie Bo; Egg Rolls; Egyptians; Ekies; Elaine; Elephants; Em; Empathy; Essence; Eve; Ex; Exiticity; Extasy; Fantasia; Fantasy; Fastin; Fizzle; Flipper; Flipping; Four leaf clover; Fuckstasy; Gaggler; Gary Ableths; Garys; Go; Googs; Green triangles; Greenies; Grey biscuits; Gum; Gumers; Gurns; GWM; Hamburger; Hamburgers; Happy drug; Happy pill; Herbal bliss; Hug drug; Hug-Drug; Huggers; Hydro; Hype; Iboga; Ice; Igloo; Illies; Jack and jills; Jellies; Jerry Garcias; Jiggas; Jills; Junnov; Khat; Kiks; Kleenex; Letter biscuits; Light meth; Lollies; Long lasting lollies; Louie Vuitton; Love-Bug; Love doctor; Love Doves; Love drug; Love drug of the '80s; Love drug of the '90s; Love heart; Love Medicine; Love pill; Love potion #9; Lovers' special; Lover's speed; Lucky charmz; "M"; M and m's; M25; Madman; Malcolm; Mandy; MAO; MDM; MDMA; Mercedes; Meth amps; Methedrine; Mini beans; Mitsi-bushis; Mitsies; Mitsu's; Mitsubishi; Mitsubishis; M&M; M&Ms; Mellow drug of America; Molly; Mollys; Monoamine oxidase; Morning shot; New yorker; New Yorkers; Nineteen; Number 9; Orange bandits; Orbit; Pasti; Pillage; Pills; Pilules d'Amour; Pingers; Pink Calis; Pink panthers; Pink studs; Play Station; Playboy bunnies; Playboys; Pollutants; Pressies; Rave energy; Red and Black; Red devils; Rhubarb and custard; Rhubarb & Custards; Rib; Ritual spirit; Road Runner; Roca; Roker's Barnet; Rolexes; Roll; Rolling; Rolls Royce; Running; Scooby snacks; Scum; Shabu; Shaking head pill; Skates; Slammin'; Slamming; Slits; Slows; Smartees; Smurfs; Speed for lovers; Spivias; Stars; Strawberry shortcake; Supermans; Swadger; Swans; Sweeties; Sweets; Tablets; Tabs; Tacha; Tachas; Tangos; Tens; The love drug; The yuppie drug; Thizz; Tom and Jerries; Triple crowns; Triple rolexes; Triple stacks; Tutus; Tweety Birds; Ultimate Xphoria; U.S.P.; Vitamin E; Vitamin X; Vowels; Wafers; Wee Boys; West Coast turnarounds; Wheels; Whiffledust; White Burger; White diamonds; White dove; White doves; Whiz bombs; Wigits; Wingers; X; X-ing; X-Men; X-Men 2; X-Pills; XTC; Yao tou wan; Yáo tóu wán; Yellow Burger; Yips; Yokes; Yuppie drug; Yuppie psychedelic; Zen.

Profile

Methylenedioxymethamfetamine is a phenylethylamine compound structurally related to amfetamine and mescaline and is an analogue of tenamfetamine (p. 2330.3). It is subject to abuse. Its toxicity is similar to that of dexamfetamine (see Abuse, below and under Dexamfetamine, p. 2319.2) and may be treated similarly.

Abuse. Methylenedioxymethamfetamine may be ingested as tablets or capsules, or inhaled as a powder. It is often mixed with adulterants such as other amfetamines, caffeine, ephedrine, and pseudoephedrine.[1]

The toxicity associated with abuse of methylenedioxymethamfetamine has been discussed.[2-7] Acute effects can be severe and symptoms have included cardiac arrhythmias, fulminant hyperthermia, convulsions, disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure; fatalities may occur. Repeated use may cause hepatic damage. Psychiatric effects reported include psychosis[8-10] and depression.[9-11] Damage to central serotonergic nerves has been implicated[8-12] and hence there is some concern about the long-term effects of methylenedioxymethamfetamine abuse.[13,14] Hyponatraemia, inappropriate antidiuretic hormone secretion, and cerebral oedema have also been reported;[15-20] the severity may be increased by excessive fluid intake that is frequently advocated to prevent dehydration and hyperthermia.[18-22] Urinary retention has also been reported.[23]

There has been concern about abuse during *pregnancy*. Twelve congenital malformations, including 2 cases of congenital heart disease, have been noted among 78 liveborn infants whose mothers had taken methylenedioxymethamfetamine, often with other drugs of abuse, during their pregnancies.[24]

For reviews of the properties of other phenylethylamine compounds, see under Tenamfetamine, p. 2331.1.

1. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59**: 1067–76.
2. Henry JA. Ecstasy and the dance of death. *BMJ* 1992; **305**: 5–6.
3. Henry JA, *et al.* Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). *Lancet* 1992; **340**: 384–7.
4. O'Connor B. Hazards associated with the recreational drug 'ecstasy'. *Br J Hosp Med* 1994; **52**: 507–14.
5. McCann UD, *et al.* Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy'). *Drug Safety* 1996; **15**: 107–115.
6. Hall AP. Ecstasy and the anaesthetist. *Br J Anaesth* 1997; **79**: 697–8.
7. Schwartz RH, Miller NS. MDMA (ecstasy) and the rave: a review. *Pediatrics* 1997; **100**: 705–8.
8. McGuire P, Fahy T. Chronic paranoid psychosis after misuse of MDMA ("ecstasy"). *BMJ* 1991; **302**: 697.
9. Winstock AR. Chronic paranoid psychosis after misuse of MDMA. *BMJ* 1991; **302**: 1150–1.
10. Schifano F. Chronic atypical psychosis associated with MDMA ("ecstasy") abuse. *Lancet* 1991; **338**: 1335.
11. Benazzi F, Mazzoli M. Psychiatric illness associated with "ecstasy". *Lancet* 1991; **338**: 1520.
12. McCann UD, *et al.* Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 1998; **352**: 1433–7.
13. Green AR, Goodwin GM. Ecstasy and neurodegeneration. *BMJ* 1996; **312**: 1493–4.
14. Bolla KI, *et al.* Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology* 1998; **51**: 1532–7.
15. Maxwell DL, *et al.* Hyponatraemia and catatonic stupor after taking "ecstasy". *BMJ* 1993; **307**: 1399.
16. Kessel B. Hyponatraemia after ingestion of "ecstasy". *BMJ* 1994; **308**: 414.
17. Satchell SC, Connaughton M. Inappropriate antidiuretic hormone secretion and extreme rises in serum creatinine kinase following MDMA ingestion. *Br J Hosp Med* 1994; **51**: 495.
18. Holden R, Jackson MA. Near-fatal hyponatraemic coma due to vasopressin over-secretion after ecstasy (3,4-MDMA). *Lancet* 1996; **347**: 1052.
19. Matthai SM, *et al.* Cerebral oedema after ingestion of MDMA (ecstasy) and unrestricted intake of water. *BMJ* 1996; **312**: 1359.
20. Parr MJA, *et al.* Hyponatraemia and death after ecstasy ingestion. *Med J Aust* 1997; **166**: 136–7.
21. Cook TM. Cerebral oedema after MDMA ('ecstasy') and unrestricted water intake. *BMJ* 1996; **313**: 689.
22. Henry JA, *et al.* Low-dose MDMA ("ecstasy") induces vasopressin secretion. *Lancet* 1998; **351**: 1784.
23. Bryden AA, *et al.* Urinary retention with misuse of 'ecstasy'. *BMJ* 1995; **310**: 504.
24. McElhatton PR, *et al.* Congenital anomalies after prenatal ecstasy exposure. *Lancet* 1999; **354**: 1441–2.

Interactions. A psychotic reaction has been reported in a patient who took methylenedioxymethamfetamine while receiving therapy with *citalopram*.[1]

A patient receiving *phenelzine* and lithium therapy experienced a serotonin syndrome (p. 443.2) after ingesting methylenedioxymethamfetamine.[2] Symptoms included

markedly increased muscle tension, tremulousness, abnormal posturing, limited pain response, tachycardia, hypertension, hyperthermia, increased white blood cell count, increased creatine phosphokinase concentration, respiratory acidosis, metabolic acidosis, delirium, and agitation. Within 15 minutes of methylenedioxymethamfetamine ingestion the patient was comatose; within 5 hours the patient was alert with a normal muscle tone. An interaction between phenelzine and methylenedioxymethamfetamine was suggested as the cause of the serotonin syndrome.

A fatal serotonergic reaction to methylenedioxymethamfetamine possibly due to an interaction with *ritonavir* has been described.[3] A prolonged and exaggerated effect from a small dose of methylenedioxymethamfetamine has been reported[4] in another patient also receiving ritonavir. Although this patient was also receiving saquinavir, the authors postulated that the mechanism may be ritonavir-induced inhibition of the cytochrome P450 isoenzyme CYP2D6.

1. Lauenna H, *et al.* Interaction of serotonin reuptake inhibitor and 3,4-methylenedioxymethamphetamine? *Biol Psychiatry* 1998; 43: 923–8.
2. Kaskey GB. Possible interaction between an MAOI and "ecstasy". *Am J Psychiatry* 1992; 149: 411–12.
3. Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. *Lancet* 1998; 352: 1751–2.
4. Harrington RD, *et al.* Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and γ-hydroxybutyrate. *Arch Intern Med* 1999; 159: 2221–4.

Methylphenidate (BAN, USAN, rINN) ⊗

Méthylphénidate; Methylphenidatum; Metilfenidato; Metylfenidat; Metyylifenidaatti; Метилфенидат.

Methyl α-phenyl-2-piperidylacetate.

$C_{14}H_{19}NO_2$=233.3

CAS — 113-45-1.

ATC — N06BA04.

ATC Vet — QN06BA04.

UNII — 207ZZ9QZ49.

Methylphenidate Hydrochloride (BANM, rINNM) ⊗

Hidrocloruro de metilfenidato; Methyl Phenidate Hydrochloride; Méthylphénidate, chlorhydrate de; Methylphenidathydrochlorid; Methylphenidati hydrochloridum; Metilfenidat Hidroklorür; Metilfenidato, hidrocloruro de; Метилфенидата Гидрохлорид.

$C_{14}H_{19}NO_2$,HCl=269.8

CAS — 298-59-9; 23655-65-4.

ATC — N06BA04.

ATC Vet — QN06BA04.

UNII — 4B3SC438HI.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methylphenidate:

Kiddie cocaine; R ball; Rities; Skippy; Vitamin R; West coast.

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

Ph. Eur. 8: (Methylphenidate Hydrochloride). A white or almost white, fine crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Methylphenidate Hydrochloride). A white, odourless, fine crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; slightly soluble in acetone and in chloroform. Solutions are acid to litmus.

Uses and Administration

Methylphenidate hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions and uses similar to those of dexamfetamine (p. 2319.2). It is used in the treatment of narcolepsy (p. 2314.3) and as an adjunct to psychological, educational, and social measures in the treatment of hyperactivity disorders (below). Methylphenidate is given orally as the hydrochloride, but the transdermal patches supply methylphenidate as the base.

In the treatment of **narcolepsy** the usual oral dose of methylphenidate hydrochloride is 20 to 30 mg daily in divided doses, normally 30 to 45 minutes before meals, but the effective dose may range from 10 to 60 mg daily.

In **hyperactivity disorders** in children aged 6 years and over, the usual initial oral dose of methylphenidate hydrochloride is 5 mg once or twice daily (as an immediate-release preparation), increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily in divided doses; the *BNFC* suggests that up to 2.1 mg/kg daily (maximum of 90 mg daily) may be given under specialist supervision. Methylphenidate may be given before breakfast and lunch. A later dose can be considered if the effect wears off in the evening causing rebound hyperactivity. Treatment is not usually continued beyond puberty, however, in some patients drug therapy may be required into adulthood. In the UK NICE suggests that adults may be given the usual initial oral dose of 5 mg three times daily, increased according to response to a maximum of 100 mg daily.

Methylphenidate hydrochloride is also available as modified-release preparations for the treatment of hyperactivity disorders. Some modified-release preparations also contain immediate-release methylphenidate within the formulation. Doses of modified-release preparations may vary according to the brand chosen. Licensed doses for one brand of modified-release tablets (*Concerta*: *Janssen-Cilag, UK; McNeil, USA*) are as follows:

- children and adolescents aged 6 to 17 years and not currently taking conventional methylphenidate should be started on 18 mg once daily in the morning
- in the USA it is also licensed for use in adults: those not currently taking conventional methylphenidate should be started on 18 or 36 mg once daily in the morning
- the dose may then be increased by 18 mg at weekly intervals to a maximum of 54 mg once daily in children and adolescents in the UK; US product information permits a maximum of 72 mg once daily in those aged 13 years and over. The *BNFC* suggests that *Concerta* may be increased to 2.1 mg/kg daily (maximum 108 mg daily)
- the dose in patients already taking conventional methylphenidate should be based on their current dose although the initial dose should not exceed 72 mg once daily

Transdermal patches delivering amounts of methylphenidate ranging from 1.1 to 3.3 mg/hour are available for once-daily application in the treatment of hyperactivity disorders in children and adolescents aged 6 to 17 years. Patients should be started on the lowest strength patch regardless of any previous methylphenidate use; thereafter, doses should be individually titrated for each patient according to response and increased at weekly intervals if necessary to a maximum of 3.3 mg/hour (at week 4). Patches should be applied to the hip area 2 hours before an effect is needed and removed after a maximum of 9 hours later.

Methylphenidate should be stopped if there is no improvement in symptoms after appropriate adjustments in dosage over one month. It also needs to be stopped from time to time in those who do respond, to assess the patient's condition.

A single isomer form of methylphenidate, dexmethylphenidate (p. 2320.3) is also used for hyperactivity disorders.

References.

1. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. *Mayo Clin Proc* 2000; 75: 711–21.

Administration in children. For doses of methylphenidate hydrochloride in children and adolescents, see Uses and Administration, above.

Depression. Stimulants are no longer recommended as sole treatment for depression (p. 398.1), although they have been tried in augmenting the effect of standard antidepressants such as the SSRIs[1] in patients with refractory depressive disorders.

1. Stoll AL, *et al.* Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *J Clin Psychiatry* 1996; 57: 72–6.

Disturbed behaviour. Disturbed behaviour can have several causes and is usually treated with an antipsychotic or benzodiazepine (see p. 1030.2). A review[1] of the published clinical studies between 1966 and June 2004 found that although methylphenidate was likely to improve memory, attention, concentration, and mental processing in patients with traumatic brain injury, its effect on behaviour remains to be determined; the most commonly used dosage was 300 micrograms/kg twice daily.

1. Siddall OM. Use of methylphenidate in traumatic brain injury. *Ann Pharmacother* 2005; 39: 1309–13.

Hyperactivity. Methylphenidate is one of the main drugs used in hyperactivity, including ADHD (p. 2314.1).

Small studies have indicated that different aspects of attention deficit disorders in children might respond to different doses of methylphenidate.[1-4] In addition to the morning and noon doses commonly used in hyperactivity disorders, studies[5,6] have shown improved clinical outcome with little adverse effect on sleep patterns if a third late afternoon dose is given.

Modified-release preparations with a slow onset of action have been developed to overcome the short duration of action of methylphenidate although they may be less effective than immediate-release preparations. A study,[7] using a regimen to simulate the prolonged steady plasma concentration profile obtained with the slow-onset, modified-release preparations, has suggested that unlike twice-daily treatment acute tolerance might develop with the use of modified-release preparations. However, some modified-release preparations that also consist of an immediate-release component have been reported to be as effective as an immediate-release preparation in short-term studies.[8-11] Transdermal patches containing methylphenidate released over 9 hours are available in the USA.[12-14]

UK guidelines for the use of methylphenidate in children and adolescents with ADHD are available.[15]

1. Sprague RL, Sleator EK. Methylphenidate in hyperkinetic children: differences in dose effects on learning and social behavior. *Science* 1977; 198: 1274–6.
2. Tannock R, *et al.* Dose-response effects of methylphenidate on academic performance and overt behavior in hyperactive children. *Pediatrics* 1989; 84: 648–57.
3. Sebrechts MM, *et al.* Components of attention, methylphenidate dosage, and blood levels in children with attention deficit disorder. *Pediatrics* 1986; 77: 222–8.
4. Barkley RA, *et al.* Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics* 1991; 87: 519–31.
5. Kent JD, *et al.* Effects of late-afternoon methylphenidate administration on behavior and sleep in attention-deficit hyperactivity disorders. *Pediatrics* 1995; 96: 320–5.
6. Stein MA, *et al.* Methylphenidate dosing: twice daily versus three times daily. *Pediatrics* 1996; 98: 748–56.
7. Swanson J, *et al.* Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 1999; 66: 295–305.
8. Pelham WE, *et al.* Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Abstract: *Pediatrics* 2001; 107: 1417. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/6/e105 (accessed 15/04/04)
9. Wolraich ML, *et al.* Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2001; 108: 883–92.
10. Reimherr FW, *et al.* A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. *J Clin Psychiatry* 2007; 68: 93–101.
11. Jain U, *et al.* Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 2007; 68: 268–77.
12. Anderson VR, Scott LJ. Methylphenidate transdermal system: in attention-deficit hyperactivity disorder in children. *Drugs* 2006; 66: 1117–26.
13. Arnold LE, *et al.* Treating attention-deficit/hyperactivity disorder with a stimulant transdermal patch: the clinical art. *Pediatrics* 2007; 120: 1100–6.
14. Findling RL, *et al.* A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2008; 69: 149–59. Correction. *ibid.*; 329.
15. NICE. Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents: review of Technology Appraisal 13 (Technology Appraisal 98, issued March 2006, reviewed March 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/TA098guidance.pdf (accessed 11/08/08)

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2. Hypersensitivity reactions have been reported. Skin reactions have included exfoliative dermatitis and erythema multiforme. Purpura, thrombocytopenia, and leucopenia have occurred. Blood counts should be monitored periodically during prolonged therapy.

Local reactions such as rash, skin irritation, redness, and itching have been reported with transdermal use.

References.

1. Ahmann PA, *et al.* Placebo-controlled evaluation of Ritalin side effects. *Pediatrics* 1993; 91: 1101–6.
2. Efron D, *et al.* Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 1997; 100: 662–6.
3. Rappley MD. Safety issues in the use of methylphenidate: an American perspective. *Drug Safety* 1997; 17: 143–8.
4. Klein-Schwartz W. Abuse and toxicity of methylphenidate. *Curr Opin Pediatr* 2002; 14: 219–23.
5. Leonard BE, *et al.* Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. *Hum Psychopharmacol* 2004; 19: 151–80.

Abuse. Reports of adverse effects after the abuse of methylphenidate by injecting solutions of crushed tablets.[1-3] Intravenous abuse of methylphenidate with pentazocine has also been reported.[4,5] In addition, there are also reports of intranasal methylphenidate abuse,[6-8] including fatalities.[8]

See also Effects on the Liver, p. 2327.1.

1. Wolf J, *et al.* Eosinophilic syndrome with methylphenidate abuse. *Ann Intern Med* 1978; 89: 224–5.
2. Gunby P. Methylphenidate abuse produces retinopathy. *JAMA* 1979; 241: 546.
3. Parran TV, Jasinski DR. Intravenous methylphenidate abuse: prototype for prescription drug abuse. *Arch Intern Med* 1991; 151: 781–3.
4. Debooy VD, *et al.* Intravenous pentazocine and methylphenidate abuse during pregnancy: maternal lifestyle and infant outcome. *Am J Dis Child* 1993; 147: 1062–5.
5. Carter HS, Watson WA. IV pentazocine/methylphenidate abuse—the clinical toxicity of another Ts and blues combination. *J Toxicol Clin Toxicol* 1994; 32: 541–7.
6. Jaffe SL. Intranasal abuse of prescribed methylphenidate by an alcohol and drug abusing adolescent with ADHD. *J Am Acad Child Adolesc Psychiatry* 1991; 30: 773–5.
7. Garland EJ. Intranasal abuse of prescribed methylphenidate. *J Am Acad Child Adolesc Psychiatry* 1998; 37: 573–4.
8. Massello W, Carpenter DA. A fatality due to the intranasal abuse of methylphenidate (Ritalin). *J Forensic Sci* 1999; 44: 220–1.

Breast feeding. No adverse effects were noted[1] in a 6-month-old breast-fed infant whose 26-year-old mother had been taking methylphenidate 40 mg twice daily for

about 5 weeks. Despite the relatively high milk-to-plasma ratio of 2.7 the relative infant dose was low, at 0.2% of the maternal dose. Nonetheless the authors recommended caution when giving methylphenidate to breast-feeding mothers. Licensed product information also recommends that methylphenidate should be used with caution or avoided during breast feeding.

1. Hackett LP, *et al.* Methylphenidate and breast-feeding. *Ann Pharmacother* 2006; 40: 1890–1.

Effects on the cardiovascular system. For mention of the adverse cardiovascular effects of stimulants, see under Dexamfetamine Sulfate, p. 2319.3.

Effects on growth. Concern has been expressed about the effects of central stimulants such as methylphenidate on growth rate when used to treat hyperactivity in children. One study showed that methylphenidate produced decreases in weight percentiles after 1 year of therapy and progressive decrement in height percentiles that became significant after 2 years of use.[1] However, another suggested that moderate doses might have a lower risk for long-term height suppression than dexamfetamine.[2] There has also been a study which showed that, even when methylphenidate had an adverse effect on growth rate during active treatment, final height was not compromised and that a compensatory rebound of growth appeared to occur on stopping stimulant treatment.[3] Height and weight should be monitored during treatment with methylphenidate.

See also under Dexamfetamine Sulfate, p. 2320.1.

1. Mattes JA, Gittelman R. Growth of hyperactive children on maintenance regimen of methylphenidate. *Arch Gen Psychiatry* 1983; 40: 317–21.
2. Greenhill LL, *et al.* Prolactin, growth hormone and growth responses in boys with attention deficit disorder and hyperactivity treated with methylphenidate. *J Am Acad Child Psychiatry* 1984; 23: 58–67.
3. Klein RG, Mannuzza S. Hyperactive boys almost grown up III: methylphenidate effects on ultimate height. *Arch Gen Psychiatry* 1988; 45: 1131–4.

Effects on the liver. Hepatotoxicity with raised liver enzyme values in a 67-year-old woman was associated with the oral use of methylphenidate hydrochloride 30 mg daily.[1] Methylphenidate-induced hepatocellular injury was reported in a 19-year-old woman who developed jaundice, fever, and malaise after intravenous abuse of methylphenidate hydrochloride tablets.[2]

1. Goodman CR. Hepatotoxicity due to methylphenidate hydrochloride. *N Y State J Med* 1972; 72: 2339–40.
2. Mehta H, *et al.* Hepatic dysfunction due to intravenous abuse of methylphenidate hydrochloride. *J Clin Gastroenterol* 1984; 6: 149–51.

Effects on mental state. Hallucinations (visual and haptic) occurred in 3 patients treated with methylphenidate.[1] All cases resolved promptly after treatment with methylphenidate was stopped.

1. Gross-Tsur V, *et al.* Hallucinations during methylphenidate therapy. *Neurology* 2004; 63: 753–4.

Effects on sexual function. Withdrawal of modified-release preparations of methylphenidate has been associated with priapism. A 15-year-old boy[1] had priapism during his weekly scheduled 24-hour withdrawal of methylphenidate; he also sometimes had erections during the school week that were relieved when he took his morning dose of methylphenidate. In another case, a 16-year-old boy[2] had priapism whenever he forgot to take his medication, which would resolve when he took his next dose.

1. Schwartz RH, Rushton HG. Stuttering priapism associated with withdrawal from sustained-release methylphenidate. *J Pediatr* 2004; 144: 675–6.
2. Health Canada. Extended-release methylphenidate (Concerta) withdrawal: suspected association with priapism. *Can Adverse React News* 2006; 16: 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n3-eng.php (accessed 04/02/10)

Effects on the skin. A fixed drug eruption of the scrotum has been reported in 2 children treated with methylphenidate for attention deficit disorder.[1]

1. Cohen HA, *et al.* Fixed drug eruption of the scrotum due to methylphenidate. *Ann Pharmacother* 1992; 26: 1378–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methylphenidate 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 25/10/11)

Tourette's syndrome. For a discussion on whether central stimulants provoke Tourette's syndrome, see Dexamfetamine Sulfate, p. 2320.2.

Interactions

As for Dexamfetamine Sulfate, p. 2320.2.

Anticoagulants. For the effect of methylphenidate on *ethyl biscoumacetate*, see Central Stimulants under the Interactions of Warfarin, p. 1533.2.

Antidepressants. For the effect of methylphenidate on *tricyclic antidepressants*, see under Amitriptyline, p. 406.1.

Antiepileptics. Methylphenidate blood concentrations decreased, and symptoms of attention deficit hyperactivity disorder worsened, in a 13-year-old girl after starting therapy with *carbamazepine*.[1]

For the effect of stimulants, such as methylphenidate on antiepileptics, see under Phenytoin, p. 545.1.

1. Schaller JL, *et al.* Carbamazepine and methylphenidate in ADHD. *J Am Acad Child Adolesc Psychiatry* 1999; 38: 112–13.

Pharmacokinetics

Methylphenidate is readily absorbed from the gastrointestinal tract. The presence of food in the stomach accelerates the rate of absorption but not the total amount absorbed. Methylphenidate undergoes extensive first-pass metabolism and peak plasma concentrations occur about 2 hours after oral doses of immediate-release preparations. The first-pass effect is less with transdermal patches, which are designed to release a stated amount of drug over 9 hours. Protein binding is low. It is excreted as metabolites mainly in the urine with small amounts appearing in the faeces; less than 1% appears in the urine as unchanged methylphenidate. The major metabolite is ritallinic acid (2-phenyl-2-piperidyl acetic acid). The plasma elimination half-life is about 2 hours after oral doses, and about 3 to 4 hours after removal of the patch. Methylphenidate is distributed into breast milk.

References.

1. Aoyama T, *et al.* Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers. *Eur J Clin Pharmacol* 1993; 44: 79–84.
2. Aoyama T, *et al.* Pharmacokinetics and pharmacodynamics of (+)-threo-methylphenidate enantiomer in patients with hypersomnia. *Clin Pharmacol Ther* 1994; 55: 270–6.
3. Shader RI, *et al.* Population pharmacokinetics of methylphenidate in children with attention-deficit hyperactivity disorder. *J Clin Pharmacol* 1999; 39: 775–785.
4. Kimko HC, *et al.* Pharmacokinetics and clinical effectiveness of methylphenidate. *Clin Pharmacokinet* 1999; 37: 457–70.
5. Modi NB, *et al.* Single- and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS (methylphenidate HCl) formulation. *J Clin Pharmacol* 2000; 40: 379–88.
6. Teo SK, *et al.* A single-dose, two-way crossover, bioequivalence study of dexmethylphenidate HCl with and without food in healthy subjects. *J Clin Pharmacol* 2004; 44: 173–8.
7. Quinn D, *et al.* Single-dose pharmacokinetics of multilayer-release methylphenidate and immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Clin Pharmacol* 2007; 47: 760–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Concerta; Methylin; Ritalina; Rubifen; *Austral.*: Attenta; Concerta; Ritalin; *Austria*: Concerta; Medikinet; Ritalin; *Belg.*: Concerta; Rilatine; *Braz.*: Concerta; Ritalina; *Canad.*: Biphentin; Concerta; Ritalin; *Chile*: Aradix; Concerta; Nebapul; Ritalin; Ritrocel†; *China*: Concerta (专注达); Cz.: Concerta; Medikinet; Ritalin; *Denm.*: Concerta; Equasym; Medikinet; Motiron; Ritalin; *Fin.*: Concerta; Equasym; Medikinet; Ritalin; *Fr.*: Concerta; Ritaline; *Ger.*: Concerta; Equasym; Medikinet; Methylpheni; Ritalin; *Gr.*: Concerta; Equasym†; Ritalin; *Hong Kong*: Concerta; Ritalin; *Hung.*: Ritalin; *India*: Addwize; Inspiral; *Indon.*: Concerta; Prohiper; Ritalin; *Irl.*: Concerta; Equasym; Medikinet; Ritalin; *Israel*: Concerta; Medikinet; Ritalin; *Ital.*: Ritalin; *Malaysia*: Concerta; Ritalin; Rubifen; *Mex.*: Concerta; Metadate; Ritalin; Tradea; *Neth.*: Concerta; Equasym; *Medikinet*; Ritalin; Tifinidat†; *Norw.*: Concerta; Equasym; Medikinet; Ritalin; *NZ*: Concerta; Ritalin; Rubifen; *Philipp.*: Concerta; Ritalin; *Pol.*: Concerta; Medikinet; *Port.*: Concerta; Ritalina; Rubifen; *S.Afr.*: Adaphen†; Concerta; Ritalin; *Singapore*: Concerta; Ritalin; Rubifen; *Spain*: Concerta; Equasym; Medicebran; Medikinet; Omozin†; Rubifen; *Swed.*: Concerta; Equasym; Medikinet; Ritalin; *Switz.*: Concerta; Medikinet; Ritaline; *Thai.*: Concerta; Ritalin; *Turk.*: Concerta; Ritaline; *UK*: Concerta; Equasym; Medikinet; Ritalin; *USA*: Concerta; Daytrana; Metadate; Methylin; Quillivant; Ritalin; *Venez.*: Concerta; Ritalin.

Pharmacopoeial Preparations

USP 36: Methylphenidate Hydrochloride Extended-release Tablets; Methylphenidate Hydrochloride Tablets.

Modafinil (BAN, USAN, rINN) ⊗

CEP-1538; CRL-40476; Modafinilo; Modafinilum; Модафинил.

2-[(Diphenylmethyl)sulfinyl]acetamide.

$C_{15}H_{15}NO_2S$=273.4

CAS — 68693-11-8.

ATC — N06BA07.

ATC Vet — QN06BA07.

UNII — R3UK8X3U3D.

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

Ph. Eur. 8: (Modafinil). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble or practically insoluble in water; sparingly soluble in methyl alcohol; slightly soluble in alcohol.

USP 36: (Modafinil). A white, odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Modafinil is a central stimulant chemically related to adrafinil (p. 2315.3). It is used in the treatment of excessive daytime sleepiness associated with the narcoleptic syndrome (p. 2314.3). The usual oral dose is 200 to 400 mg daily, in two divided doses, in the morning and at midday, or as a single dose in the morning. An initial dose of 100 mg daily should be used in the elderly and adjusted as necessary. For doses in hepatic impairment, see below.

Modafinil has also been used in oral doses of 200 mg daily for the treatment of obstructive sleep apnoea/hypopnoea syndrome and shift-work sleep disorder although in 2010 the EMEA recommended that such indications be removed from marketing authorisations (see p. 2328.1). For the treatment of obstructive sleep apnoea/hypopnoea syndrome, the daily dose should be taken in the morning and for shift-work sleep disorder, the daily dose should be taken as a single dose 1 hour before starting work.

Modafinil is usually given as a racemic mixture but preparations containing only the *R*-isomer, armodafinil, are also available, see Armodafinil, p. 2316.3.

Modafinil has also been investigated for the treatment of fatigue associated with various disorders including multiple sclerosis and for the treatment of hyperactivity disorders.

References.

1. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* 2000; 54: 1166–75.
2. Kingshott RN, *et al.* Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 2001; 163: 918–23.
3. Czeisler CA, *et al.* The US Modafinil in Shift Work Sleep Disorder Study Group. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med* 2005; 353: 476–86. Correction. *ibid.*; 1078.
4. Gill M, *et al.* Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. *Acad Emerg Med* 2006; 13: 158–65. Correction. *ibid.*; 477.
5. Turner D. A review of the use of modafinil for attention-deficit hyperactivity disorder. *Expert Rev Neurother* 2006; 6: 455–68.
6. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry* 2006; 67: 554–66.
7. Lindsay SE, *et al.* Use of modafinil for the treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother* 2006; 40: 1829–33.
8. Kumar R. Approved and investigational uses of modafinil: an evidence-based review. *Drugs* 2008; 68: 1803–39.

Administration in hepatic impairment. UK licensed product information states that the total oral dose of modafinil (see Uses and Administration, above) should be reduced by half in patients with severe hepatic impairment.

Adverse Effects, Treatment, and Precautions

The most commonly reported adverse effect of modafinil, affecting about 21% of patients, is headache, which is usually mild or moderate, dose-dependent, and disappears within a few days. Other adverse effects may be a result of CNS stimulation and effects such as nervousness, insomnia, agitation, confusion, personality disorder, tremor, and anxiety have been noted. There may also be gastrointestinal disturbances, including nausea and abdominal pain, dry mouth, diarrhoea, dyspepsia, and constipation, dizziness, and anorexia. Abnormal liver function tests including dose-related increases in alkaline phosphatase, and dyskinesia have been seen.

Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis, have been reported (see also Effects on the Skin, p. 2328.1). Benign pruritic rashes have also occurred and since it is not possible to predict which rashes will become serious, modafinil should be stopped at the first sign of rash unless it is clearly not drug-related. Other hypersensitivity reactions such as angioedema have also been reported rarely.

Psychiatric symptoms including psychosis, depression, hallucinations, suicidal ideation, and mania have been reported. Modafinil should be given with caution to those with a history of psychosis, depression, or mania.

Cardiovascular effects such as hypertension, palpitations, and tachycardia have been reported. Modafinil is contra-indicated in patients with uncontrolled, moderate to severe hypertension or cardiac arrhythmias. It is not recommended in patients with a history of left ventricular hypertrophy or ischaemic ECG changes, chest pain, or other signs of mitral valve prolapse.

As with other stimulants, there is the possibility of dependence with long-term use. Modafinil has been misused as a so-called 'lifestyle drug' to promote alertness and wakefulness in otherwise healthy subjects.

In July 2010, the EMEA's Committee for Medicinal Products for Human Use (CHMP) reported on its safety review of modafinil.[1] The committee concluded that the benefits of modafinil only outweighed the risks in narcolepsy. For all other indications the risk of developing skin or hypersensitivity reactions and neuropsychiatric disorders outweighed efficacy. Therefore, the CHMP concluded that all indications except narcolepsy should be withdrawn from the marketing authorisations for modafinil.

1. EMEA. European Medicines Agency recommends restricting the use of modafinil (issued 22 July, 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/07/WC500094976.pdf (accessed 09/08/10)

Effects on mental state. The Australian Adverse Drug Reactions Advisory Committee[1] reported that it had been notified of 5 cases of serious psychiatric reactions associated with modafinil since 2003. All patients had a history of paranoid personality, depression, or post-natal depression. The presenting symptoms were anxiety, abnormal behaviour, guilt feelings, rapid relapse/onset of depression, suicidal ideation, suicidal behaviour, psychotic disorder, and delusion. In 3 cases, the reaction occurred after only a few doses but in the other 2 cases onset was over 1 year after the drug was started. All cases resolved when modafinil was stopped; re-challenge was positive in one case of depression. See also above.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Modafinil: adverse skin and psychiatric reactions. *Aust Adverse Drug React Bull* 2008; 27: 22–3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0812.pdf (accessed 20/01/10)

Effects on the skin. The FDA[1] reported that it had received 6 cases of severe cutaneous adverse effects associated with modafinil from its initial marketing in December 1998 to January 2007; of these, 5 required hospitalisation. The cutaneous effects, which included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms, were reported in adults and children although use in patients under 16 years of age is unlicensed. The median time to onset was 17.5 days with a range of 5 days to 5 weeks. See also above.

1. Modafinil (marketed as Provigil): serious skin reactions. *FDA Drug Safety Newsletter* 2007; 1: 5–7. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109158.pdf (accessed 26/01/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies modafinil 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 25/10/11)

Interactions

Modafinil is partially metabolised by cytochrome P450 isoenzymes. In addition, it also has enzyme-inducing and -inhibiting activity. Use with other drugs that inhibit, induce, or act as a substrate to these isoenzymes such as oral contraceptives and antiepileptics may result in changes in plasma concentration of modafinil and/or the other drug.

Pharmacokinetics

Modafinil is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after oral doses. Plasma protein binding is about 60%, mainly to albumin. Modafinil is metabolised in the liver, partially by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5; two major metabolites have been identified: acid modafinil and modafinil sulfone, both of which are inactive. Excretion is mainly through the kidneys with less than 10% of the dose being eliminated unchanged. The elimination half-life after multiple doses is 15 hours.

References.
1. Wong YN, *et al.* A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. *J Clin Pharmacol* 1999; 39: 30–40.
2. Wong YN, *et al.* Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. *J Clin Pharmacol* 1999; 39: 281–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Forcilin; Intensit; Nopral; Vigicer; *Austral.*: Modavigil; *Austria*: Modasomil; *Belg.*: Provigil; *Braz.*: Stavigile; *Canad.*: Alertec; *Chile*: Alertex; Mentix; Movigil; Naxelan; Resotyl; Zalux; *Cz.*: Vigil; *Denm.*: Modiodal; Provigil†; *Fr.*: Modiodal; *Ger.*: Vigil; *Gr.*: Modiodal; *Hung.*: Vigil; *India*: Modalert; Modfil; *Irl.*: Provigil; *Israel*: Provigil; *Ital.*: Provigil; *Jpn*: Modiodal; *Mex.*: Modiodal; *Neth.*: Aspendos; Modiodal; *Norw.*: Modiodal; *NZ*: Modavigil; *Pol.*: Vigil†; *Port.*: Modiodal; *S.Afr.*: Provigil; *Spain*: Modiodal; *Swed.*: Modiodal; *Switz.*: Modasomil; *Turk.*: Modiodal; *UK*: Provigil; *USA*: Provigil.

Pharmacopoeial Preparations
USP 36: Modafinil Tablets.

Naphyrone ⊗

Naphthylpyrovalerone; NRG-1; O-2482.
1-(2-Napthalenyl)-2-(1-pyrrolidinyl)-1-pentanone.
$C_{19}H_{23}NO$=281.4
CAS — 850352-53-3 (naphyrone); 850352-11-3 (naphyrone hydrochloride).

NOTE. The term NRG-1 has also been applied to the protein Neuroregulin 1.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of naphyrone:
Energy-1; Rave.

Profile

Naphyrone, a derivative of pyrovalerone, is reported to have stimulant properties and is subject to abuse (see also Abuse, under Catha, p. 2318.3).

Nikethamide (BAN, rINN) ⊗

Cordiaminum; Nicetamid; Nicethamid; Nicéthamide; Nicethamidum; Nicotinic Acid Diethylamide; Nicotinoyldiaethylamidum; Niketamid; Niketamidas; Niketamidi; Nikethamid; Nikethylamide; Niquetamida; Никетамид.
N,N-Diethylnicotinamide; *N,N*-Diethylpyridine-3-carboxamide.
$C_{10}H_{14}N_2O$=178.2
CAS — 59-26-7.
ATC — R07AB02.
ATC Vet — QR07AB02.
UNII — 368IVD6M32.

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

Ph. Eur. 8: (Nikethamide). A colourless or slightly yellow oily liquid or crystalline mass. Miscible with water and with alcohol. A 25% solution in water has a pH of 6.0 to 7.8.

Profile

Nikethamide has actions similar to those of doxapram (p. 2321.2). It was formerly used as a respiratory stimulant but has largely been abandoned because of toxicity. Nikethamide and its calcium thiocyanate salt have also been used in some countries as central stimulants and for hypotensive disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Cardiamidum.

Multi-ingredient Preparations. *Fr.*: Coramine Glucose; *Pol.*: Cardiamid-Coffein†; Glucardiamid; *Switz.*: Gly-Coramin.

Pharmacopoeial Preparations
BP 2014: Nikethamide Injection.

Pemoline (BAN, USAN, rINN) ⊗

Fenoxazol; LA-956; NSC-25159; Pemoliini; Pemolin; Pemolina; Pémoline; Pemolinum; Phenoxazole; Phenylisohydantoin; Phenylpseudohydantoin; Пемолин.
2-Imino-5-phenyl-4-oxazolidinone.
$C_9H_8N_2O_2$=176.2
CAS — 2152-34-3 (pemoline); 68942-31-4 (pemoline hydrochloride); 18968-99-5 (magnesium pemoline).
ATC — N06BA05.
ATC Vet — QN06BA05.
UNII — 7GAQ2332NK.

Profile

Pemoline is a central stimulant with actions similar to those of dexamfetamine (p. 2319.1).

It has been used in the management of hyperactivity disorders in children; however, in many countries it was withdrawn from such use after reports of serious hepatotoxicity. Hypertensive crisis may possibly occur if pemoline is given with MAOIs.

Pemoline has been included in preparations also containing yohimbine hydrochloride and methyltestosterone that are claimed to combat failure of sexual desire and functioning in males and females; such preparations are not recommended.

Pemoline has been given with magnesium hydroxide (magnesium pemoline) in an attempt to increase its absorption.

Abuse. Paranoid psychosis occurred in a 38-year-old man taking pemoline 75 to 225 mg daily.[1] His compulsive use of the drug, development of tolerance, depressive withdrawal syndrome, and inability to abstain indicated dependence and it was evident that the patient was addicted to pemoline.

Choreoathetosis and rhabdomyolysis developed in a patient after a marked increase in intake of pemoline.[2] Abnormal movements responded to diazepam.

1. Polchert SE, Morse RM. Pemoline abuse. *JAMA* 1985; 254: 946–7.
2. Briscoe JG, *et al.* Pemoline-induced choreoathetosis and rhabdomyolysis. *Med Toxicol* 1988; 3: 72–6.

Effects on the liver. Pemoline has been associated with hepatotoxicity.

Elevated concentrations of serum aspartate aminotransferase and serum alanine aminotransferase have been noted in 2% of children taking pemoline for hyperactivity; the effect was stated to be transient and reversible.[1]

However, more serious reactions have also occurred. Acute hepatitis[2] was associated with pemoline in a 10-year-old boy and the drug was believed to be the cause of fatal fulminant liver failure[3] in a 14-year-old boy and in 2 previously published cases. The UK CSM[4] subsequently became aware of 33 reports of serious hepatic reactions in the USA, including a total of 6 fatalities and the need for liver transplantation in 2 cases; this prompted the withdrawal of pemoline for the treatment of hyperactivity in the UK. Following further reports of liver failure resulting in transplantation or death, the FDA[5] similarly withdrew pemoline in the USA.

1. Anonymous. Hyperkinesis' can have many causes, symptoms. *JAMA* 1975; 232: 1204–16.
2. Patterson JF. Hepatitis associated with pemoline. *South Med J* 1984; 77: 938.
3. Berkovitch M, *et al.* Pemoline-associated fulminant liver failure: testing the evidence for causation. *Clin Pharmacol Ther* 1995; 57: 696–8.
4. CSM/MCA. Volital (pemoline) has been withdrawn. *Current Problems* 1997; 23: 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 23/05/06)
5. FDA. Alert for healthcare professionals: pemoline tablets and chewable tablets (marketed as Cylert) (issued October, 2005). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126462.pdf (accessed 09/04/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Ceractiv; Cylert†; *Israel*: Nitan†.

Multi-ingredient Preparations. *UK*: Prowess.

Pentetrazol (BAN, rINN) ⊗

Corazol; Leptazol; Pentamethazol; 1,5-Pentamethylenetetrazole; Pentazol; Pentetrasoli; Pentétrazol; Pentetrazolum; Pentylenetetrazol; Пентетразол.
6,7,8,9-Tetrahydro-5*H*-tetrazoloazepine.
$C_6H_{10}N_4$=138.2
CAS — 54-95-5.
ATC — R07AB03.
ATC Vet — QR07AB03.
UNII — WM5Z385K7T.

Pharmacopoeias. In *It.*

Profile

Pentetrazol is a central and respiratory stimulant similar to doxapram (p. 2321.2). It has been used in respiratory depression and in multi-ingredient preparations intended for the treatment of respiratory-tract disorders including cough, cardiovascular disorders including hypotension, and for the treatment of pruritus. It has been given orally and by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Cardiazol-Paracodina; *Port.*: Broncodiazina†.

Phendimetrazine Tartrate (BANM, rINNM) ⊗

Fendimetrazina, tartrato de; Phendimétrazine Acid Tartrate; Phendimetrazine Bitartrate; Phendimétrazine, Tartrate de; Phendimetrazini Tartras; Tartrato de fendimetrazina; Фендиметразина Тартрат.
(+)-3,4-Dimethyl-2-phenylmorpholine hydrogen tartrate.

$C_{12}H_{17}NO.C_4H_6O_6$=341.4.
CAS — 634-03-7 (phendimetrazine); 7635-51-0 (phendimetrazine hydrochloride); 50-58-8 (phendimetrazine tartrate).
UNII — 6985IP0T80.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of phendimetrazine:

Fringas; Prelo.

Pharmacopoeias. In *US*.

USP 36: (Phendimetrazine Tartrate). A white odourless crystalline powder. Freely soluble in water; sparingly soluble in warm alcohol; insoluble in acetone, in chloroform, in ether, and in benzene. pH of a 2.5% solution in water is between 3.0 and 4.0. Store in airtight containers.

Uses and Administration

Phendimetrazine tartrate is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.2). It has been used as an anorectic in the short-term treatment of obesity (p. 2315.1), although stimulants are no longer recommended for this indication. The usual oral dose is 35 mg two or three times daily before food. An alternative dose is 105 mg once daily in the morning as a modified-release preparation.

Phendimetrazine hydrochloride has been used similarly.

Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2.

Pulmonary hypertension and valvular heart defects have been reported in patients receiving phendimetrazine with other anorectics; these adverse effects, with the relevant precautions to be observed, are discussed under Fenfluramine Hydrochloride (see Effects on the Cardiovascular System, p. 2322.3). Phendimetrazine should not be used with other anorectics nor within a year of their use.

Interactions

Phendimetrazine is an indirect-acting sympathomimetic and may interact with other drugs similarly to dexamfetamine (p. 2320.2).

Pharmacokinetics

Phendimetrazine tartrate is readily absorbed from the gastrointestinal tract and is excreted in the urine, partly unchanged and partly as phenmetrazine and other metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *S.Afr.*: Obesan-X; Obex-LA; *USA*: Bontril; Melfiat; Prelu-2.

Pharmacopoeial Preparations
USP 36: Phendimetrazine Tartrate Capsules; Phendimetrazine Tartrate Tablets.

Phenmetrazine Hydrochloride

(BANM, rINNM) ⊗

Fenmetrazina, hidrocloruro de; Hidrocloruro de fenmetrazina; Oxazimédrine; Phenmétrazine, Chlorhydrate de; Phenmetrazini Hydrochloridum; Фенметразина Гидрохлорид.

(±)-*trans*-3-Methyl-2-phenylmorpholine hydrochloride.

$C_{11}H_{15}NO.HCl$=213.7.
CAS — 134-49-6 (phenmetrazine); 1707-14-8 (phenmetrazine hydrochloride); 13931-75-4 (phenmetrazine teoclate).
UNII — 6U8SYR1588.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of Phenmetrazine:

Preludes.

Pharmacopoeias. In *US*.

USP 36: (Phenmetrazine Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 0.4 of water, 1 in 2 of alcohol, and 1 in 2 of chloroform. pH of a 2.5% solution in water is between 4.5 and 5.5. Store in airtight containers.

Profile

Phenmetrazine hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.1). It has been used as an anorectic in the treatment of obesity. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3). It has been subject to extensive abuse.

Abuse. For reference to a serious syndrome involving rhabdomyolysis after intravenous abuse of phenmetrazine, see Dexamfetamine Sulfate, p. 2319.3.

Preparations

Pharmacopoeial Preparations
USP 36: Phenmetrazine Hydrochloride Tablets.

Phentermine *(BAN, USAN, rINN)* ⊗

Fentermiini; Fentermin; Fentermina; Phenterminum; Фентермин.

α,α-Dimethylphenethylamine.

$C_{10}H_{15}N$=149.2
CAS — 122-09-8.
ATC — A08AA01.
ATC Vet — QA08AA01.
UNII — C045TQL4WP.

Phentermine Hydrochloride *(BANM, rINNM)* ⊗

Fentermina, hidrocloruro de; Hidrocloruro de fentermina; Phentermine, Chlorhydrate de; Phentermini Hydrochloridum; Фентермина Гидрохлорид.

$C_{10}H_{15}N.HCl$=185.7
CAS — 1197-21-3.
ATC — A08AA01.
ATC Vet — QA08AA01.
UNII — 0K2I50SOTV.

Pharmacopoeias. In *US*.

USP 36: (Phentermine Hydrochloride). A white, odourless, hygroscopic, crystalline powder. Soluble in water and in the lower alcohols; slightly soluble in chloroform; insoluble in ether. pH of a 2% solution in water is between 5.0 and 6.0. Store in airtight containers.

Uses and Administration

Phentermine is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.2). It has been used as an anorectic in the short-term treatment of moderate to severe obesity (p. 2315.1), although stimulants are no longer recommended for this indication; it may also be used in overweight patients (BMI of 27 kg/m² or more) if other risk factors such as hypertension, diabetes mellitus, or dyslipidaemia are present. Phentermine is given orally as the hydrochloride or the base; phentermine hydrochloride 15 mg is equivalent to about 12 mg of phentermine.

The usual dose of phentermine hydrochloride ranges from 15 to 37.5 mg daily given as a single dose before or after breakfast; alternatively, the higher dose of 37.5 mg daily may be given in 2 divided doses. Phentermine base is given as a modified-release, ion-exchange resin complex in a usual dose of 15 or 30 mg once daily before breakfast or 10 to 14 hours before bedtime.

A once-daily modified-release combination preparation containing phentermine hydrochloride and topiramate (p. 551.1) is also available. The recommended initial dose is the equivalent of phentermine 3.75 mg with topiramate 23 mg daily in the morning; after 14 days, this may be increased to phentermine 7.5 mg/topiramate 46 mg daily. If the patient has not lost at least 3% of initial body-weight after 12 weeks at this dose, treatment should be stopped or the dose further increased to phentermine 11.25 mg/topiramate 69 mg daily for 14 days, followed by phentermine 15 mg/topiramate 92 mg daily.

Treatment should be stopped if the patient has not lost at least 5% of initial body-weight after 12 weeks at the highest dose, as continued treatment is unlikely to be of benefit; withdrawal of therapy should be made gradually by taking a dose every other day for at least 1 week before stopping altogether to avoid precipitating a seizure.

Reduced doses are recommended in patients with hepatic or renal impairment, see below.

Regulatory authorities in the EU have called for the withdrawal of phentermine from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

References.
1. Cameron F, *et al.* Phentermine and topiramate extended release (Qsymia®): first global approval. *Drugs* 2012; 72: 2033–42.
2. Smith SM, *et al.* Phentermine/topiramate for the treatment of obesity. *Ann Pharmacother* 2013; 47: 340–9.
3. Cosentino G, *et al.* Phentermine and topiramate for the management of obesity: a review. *Drug Des Devel Ther* 2013; 7: 267–78.
4. Shin JH, Gadde KM. Clinical utility of phentermine/topiramate (Qsymia®) combination for the treatment of obesity. *Diabetes Metab Syndr Obes* 2013; 6: 131–9.

Administration in hepatic or renal impairment. Phentermine is excreted in the urine and increased exposure may occur in patients with renal impairment. Licensed product information recommends that the dose of the oral modified-release combination preparation should not exceed phentermine 7.5 mg/topiramate 46 mg once daily in patients with moderate hepatic (Child-Pugh score 7 to 9) or moderate to severe renal (creatinine clearance below 50 mL/min) impairment; its use is not recommended in those with severe hepatic impairment or end-stage renal impairment requiring dialysis due to a lack of data.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2. Urticaria may occur with use of phentermine.

Pulmonary hypertension has been reported in patients receiving phentermine and valvular heart defects in patients receiving the drug with other anorectics such as fenfluramine or dexfenfluramine; these adverse effects, with the relevant precautions to be observed, are discussed under Fenfluramine Hydrochloride (see Effects on the Cardiovascular System, p. 2322.3).

Treatment of overdose is largely supportive. The benefit of gastric decontamination is uncertain; however, activated charcoal may be given orally to adults or children who present within 1 hour of ingesting 1 mg/kg or more of phentermine. Lavage may be considered in adults who present within 1 hour of a potentially life-threatening overdose.

Interactions

Phentermine is an indirect-acting sympathomimetic and may interact with other drugs, similarly to dexamfetamine (p. 2320.2).

Pharmacokinetics

Phentermine is readily absorbed from the gastrointestinal tract and is excreted in the urine, partly unchanged and partly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Duromine; Metermine; *Cz.*: Adipex; *Hong Kong*: Duromine; Panbesy; Redusa; *Israel*: Razin; *Malaysia*: Adipex; Duromine; *Mex.*: Acxion; Ifa Acxion; Ifa Reducing†; Raamcap; Sinpet†; Terlamex; *NZ*: Duromine; *Philipp.*: Duromine; Supremin; *S.Afr.*: Duromine; *Singapore*: Duromine; Panbesy; Umine†; *Thai.*: Duromine; Panbesy; *USA*: Adipex-P; Ionamin†; Suprenza; *Venez.*: Mirubal.

Multi-ingredient Preparations. *USA*: Qsymia.

Pharmacopoeial Preparations
USP 36: Phentermine Hydrochloride Capsules; Phentermine Hydrochloride Tablets.

Pipradrol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pipradrol; Pipradol Hydrochloride; Pipradrol, Chlorhydrate de; Pipradrol, hidrocloruro de; Pipradroli Hydrochloridum; Пипрадрола Гидрохлорид.

α-2-Piperidylbenzhydrol hydrochloride; α,α-Diphenyl-2-piperidinemethanol hydrochloride.

$C_{18}H_{21}NO.HCl$=303.8
CAS — 467-60-7 (pipradrol); 71-78-3 (pipradrol hydrochloride).
ATC — N06BX15.
ATC Vet — QN06BX15.
UNII — F6E46VR9Y2.

Profile

Pipradrol hydrochloride has been given orally in tonic preparations as a CNS stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Alertonic; *S.Afr.*: Alertonic†.

Prethcamide ⊗

G-5668; Pretcamida; Претками́д.
CAS — 8015-51-8.
ATC — R07AB06.
ATC Vet — QR07AB06.
UNII — 41A1FCW148.

Description. Prethcamide is a mixture of equal parts by weight of cropropamide and crotetamide.

Cropropamide (BAN, pINN) ⊗

Cropropamida; Cropropamidum; Kropropamid; Kropropamidi; Кропропамид.

N,N-Dimethyl-2-(*N*-propylcrotonamido)butyramide.

$C_{13}H_{24}N_2O_2$=240.3

CAS — 633-47-6.

UNII — W8TYE9V98X.

Crotetamide (BAN, rINN) ⊗

Crotetamida; Crotétamide; Crotetamidum; Crotethamide; Кротетамид.

2-(*N*-Ethylcrotonamido)-*N,N*-dimethylbutyramide.

$C_{12}H_{22}N_2O_2$=226.3

CAS — 6168-76-9.

UNII — 642197LB5B.

Profile

Prethcamide, a mixture of equal parts by weight of cropropamide and crotetamide, has actions similar to those of doxapram (p. 2321.2) and has been used orally as a respiratory stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Micoren†.

Propylhexedrine (BAN, rINN) ⊗

Hexahydrodesoxyephedrine; Propilhexedrina; Propylhexed; Propylhexédrine; Propylhexedrinum; Пропилгекседрин.

2-Cyclohexyl-1-methylethyl-(methyl)amine; (±)-*N*-α-Dimethylcyclo-hexaneethylamine.

$C_{10}H_{21}N$=155.3

CAS — 101-40-6; 3595-11-7 ((±)-propylhexedrine).

UNII — LQU92IU8LL.

Pharmacopoeias. In *US*.

USP 36: (Propylhexedrine). A clear colourless liquid having a characteristic amine-like odour. It slowly volatilises at room temperature and absorbs carbon dioxide from the air. Very slightly soluble in water; soluble 1 in 0.4 of alcohol, 1 in 0.2 of chloroform, and 1 in 0.1 of ether. Its solutions are alkaline to litmus. Store in airtight containers.

Propylhexedrine Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de propilhexedrina; Propilhexedrina, hidrocloruro de; Propylhexédrine, Chlorhydrate de; Propylhexedrini Hydrochloridum; Пропилгекседрина Гидрохлорид.

$C_{10}H_{21}N.HCl$=191.7

CAS — 1007-33-6; 6192-95-6 ((±)-propylhexedrine hydrochloride).

UNII — 064LUN7NZS.

Uses and Administration

Propylhexedrine is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.2). It has been used as an inhalant for nasal decongestion.

Propylhexedrine hydrochloride has been given orally as an anorectic in the treatment of obesity but stimulants are no longer recommended for this indication. The (-)-isomer, levopropylhexedrine hydrochloride, has been used similarly.

Adverse Effects, Treatment and Precautions

As for Dexamfetamine Sulfate, p. 2319.2.

Nasal inhalation may cause transient burning, stinging, mucosal dryness, and sneezing. Prolonged use can cause rebound congestion, redness, swelling, and rhinitis. Systemic effects such as headache, hypertension, nervousness, and increased heart rate may occur.

Propylhexedrine is subject to oral and intravenous abuse; fatalities due to myocardial infarction, heart failure, or pulmonary hypertension have been reported. Psychosis may occur.

Abuse. References.

1. White L, DiMaio VJM. Intravenous propylhexedrine and sudden death. *N Engl J Med* 1977; 297: 1071.
2. Anderson RJ, *et al.* Intravenous propylhexedrine (Benzedrex) abuse and sudden death. *Am J Med* 1979; 67: 15–20.
3. Cameron J, *et al.* Possible association of pulmonary hypertension with an anorectic drug. *Med J Aust* 1984; 140: 595–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Benzedrex.

Pharmacopoeial Preparations

USP 36: Propylhexedrine Inhalant.

Sibutramine Hydrochloride

(BANM, USAN, rINNM) ⊗

BTS-54524; Hidrocloruro de sibutramina; Sibutramin Hidroklorür; Sibutramina, hidrocloruro de; Sibutramine, Chlorhydrate de; Sibutramini Hydrochloridum; Сибутрамина Гидрохлорид.

(±)-1-(*p*-Chlorophenyl)-α-isobutyl-*N,N*-dimethylcyclobutanemethylamine hydrochloride monohydrate.

$C_{17}H_{26}ClN.HCl.H_2O$=334.3

CAS — 106650-56-0 (sibutramine); 84485-00-7 (anhydrous sibutramine hydrochloride); 125494-59-9 (sibutramine hydrochloride monohydrate).

ATC — A08AA10.

ATC Vet — QA08AA10.

UNII — OGM0YHD1WF.

Pharmacopoeias. In *US*.

USP 36: (Sibutramine Hydrochloride). White to cream, crystalline powder. Slightly soluble in water at pH 5.2. Store in airtight containers.

Profile

Sibutramine, which is structurally related to amfetamine (p. 2316.1), is a serotonin and noradrenaline reuptake inhibitor; it also inhibits dopamine reuptake but to a lesser extent. Sibutramine has been used in the management of obesity. However, cardiovascular and cerebrovascular adverse effects, sometimes serious, including vasodilatation, cardiac arrhythmias, hypertension, myocardial infarction, and stroke, have been noted and this has led to the suspension of sibutramine in many countries (see below for further details).

References.

1. Nisoli E, Carruba MO. A benefit-risk assessment of sibutramine in the management of obesity. *Drug Safety* 2003; 26: 1027–48.
2. Vettor R, *et al.* Effect of sibutramine on weight management and metabolic control in type 2 diabetes: a meta-analysis of clinical studies. *Diabetes Care* 2005; 28: 942–9.

Adverse effects and precautions. *EFFECTS ON THE CARDIOVASCULAR SYSTEM.* In January 2010, the EMEA's Committee for Medicinal Products for Human Use (CHMP) reported on its safety review of sibutramine.[1] Data from a large study, the Sibutramine Cardiovascular OUTcomes (SCOUT) study showed an increased risk of non-fatal, but serious, cardiovascular events such as myocardial infarction and stroke in patients taking sibutramine. It was also noted that the average weight loss achieved with sibutramine in all studies was modest. Consequently, the CHMP considered that the cardiovascular risks of sibutramine outweighed its benefits and recommended that sibutramine be suspended across the EU.

The SCOUT study was a randomised, double-blind, placebo-controlled study in about 10 000 obese and overweight patients, with cardiovascular disease and/or type 2 diabetes treated over a 6-year period.[1,2] Patients treated with sibutramine had a 16% increased risk of non-fatal cardiovascular events compared with those taking placebo. Although most of the patients enrolled within the SCOUT study had contra-indications for sibutramine under normal conditions of use, the CHMP considered the cardiovascular risk to be relevant to normal clinical use because it is not always possible to identify underlying cardiovascular disease in patients who are obese or overweight. Therefore, it considered that further restrictions on the use of sibutramine would be unlikely to reduce the risk to an acceptable level.

Based on the SCOUT data, the FDA did not initially withdraw sibutramine from the US market in January 2010, but stated that it was now contra-indicated in patients with a history of cardiovascular disease. However, after further analysis[3] of the data, sibutramine was subsequently withdrawn from the US market in October 2010.

1. EMEA. The European Medicines Agency recommends suspension of marketing authorisations for sibutramine: weight-loss medicine associated with increased risk of cardiovascular events to be removed from all markets in the European Union (issued 21st January, 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/01/WC500069995.pdf (accessed 21/07/10)
2. MHRA. Sibutramine: suspension of marketing authorisation as risks outweigh benefits (issued 21st January, 2010). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON068475 (accessed 27/01/10)
3. FDA. Drug safety communication: FDA recommends against the continued use of Meridia (sibutramine) (issued 8th October, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm228746.htm#Safety_Announcement (accessed 11/10/10)

PORPHYRIA. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sibutramine 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 25/10/11)

PREGNANCY. Between May 2001 and September 2004,[1] the prospective outcomes of 52 pregnant women who were exposed to sibutramine in the first trimester of pregnancy were recorded. Hypertensive complications were seen in 7 cases but there were no cases of congenital anomalies. The authors suggest that, based on a small number of exposures, sibutramine may not be teratogenic in pregnancy.

1. De Santis M, *et al.* Early first-trimester sibutramine exposure: pregnancy outcome and neonatal follow-up. *Drug Safety* 2006; 29: 255–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aderan; Downtrat; Ipomex; Restrical; Sacietyl†; Sertinal†; Sibu-Estirol†; Sibu-Tratobes†; *Austral.*: Reductil†; *Austria*: Reductil†; *Belg.*: Reductil†; *Braz.*: Biomag; Nolipo; Plenty; Reductil†; Saciette; Sibuctil; Sibus; Sibutran; Sigran (C1); Slenfig; Vazy; *Canad.*: Meridia†; *Chile*: Adisar; Atenix; Ipogras; Medixil; Mesura; Milical; Mintagras; Noductil†; Reductil†; Reduten; Saton; *Cz.*: Lindaxa†; Meridia†; *Denm.*: Reductil†; *Fin.*: Reductil†; *Fr.*: Subutral†; *Ger.*: Reductil†; *Gr.*: Reductil†; *Hong Kong*: Reductil†; *Hung.*: Lindaxa†; Reductil†; *India*: Petrasil; Leptos; Obestat; *Indon.*: Maxislim; Reductil†; *Irl.*: Reductil†; *Israel*: Reductil†; *Ital.*: Ectiva†; Reductil†; *Malaysia*: Reductil†; *Mex.*: Adelseril; Adelvag; Ectiva; Gea; Ifa-Certez; Kifenip; Obectiv; Raductil; Randism†; Segusiv; Serotramin; Siruton; Tramentel; Vivellsi; *Neth.*: Reductil†; *Norw.*: Reductil†; *NZ*: Reductil†; *Philipp.*: Lesfat; Nobese; Reductil†; Sibutrim†; Slenfig; Zytrim†; *Pol.*: Lindaxa†; Meridia†; Zelixa†; *Port.*: Egostart†; Reductil†; Zelium†; *Rus.*: Goldline (Голдлайн); Lindaxa (Линдакса); Meridia (Меридиа); Reduksin (Редуксин); Slimia (Слимия); *S.Afr.*: Ciplatrim; Ectiva; Reductil†; *Singapore*: Ectiva†; Reductil†; Slenfig†; *Spain*: Reductil†; *Swed.*: Reductil†; *Switz.*: Reductil†; *Thal.*: Reductil†; *Turk.*: Burna; Nadyak; Reductil†; Zelium; *UK*: Reductil†; *Ukr.*: Lindaxa (Линдакса)†; Meridia (Меридиа)†; *USA*: Meridia†; *Venez.*: Milical; Reductil†; Repentil; Vintix.

Multi-ingredient Preparations. *Mex.*: Ifa-Certez Duo; Redumed.

Tenamfetamine (rINN) ⊗

MDA; 3,4-Methylenedioxyamphetamine; Methylenedioxyamphetamine; SKF-5; Ténamfétamine; Tenamfetaminum; Tenanfetamina; Тенамфетамин.

α-Methyl-3,4-methylenedioxyphenethylamine.

$C_{10}H_{13}NO_2$=179.2

CAS — 4764-17-4; 51497-09-7.

UNII — XJZ28FJ27W.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of tenamfetamine:

EA1299; Eve; Love Drug; Love Pill; MDMA; Mellow Drug of America.

Profile

Tenamfetamine is a phenylethylamine compound, structurally related to amfetamine and mescaline, with hallucinogenic effects. It has been subject to abuse and dependence. Several similar compounds are known because of their abuse and include:

- brolamfetamine (4-bromo-2,5-dimethoxyamfetamine; bromo-DMA; bromo-DOM; 2,5-dimethoxy-4-bromoamfetamine; DOB)
- 4-bromo-2,5-dimethoxyphenylethylamine (2's; Afterburner; BDMPEA; Bees; Bromo; Bromo Mescaline; 2-CB; MFT; Nexus; Spectrum; Toonies; Venus)
- 2,5-dimethoxy-4-metamfetamine (DOM; 4-methyl-2,5-dimethoxyamfetamine; Serenity, Tranquillity and Peace; STP)
- 3,4-methylenedioxyethylamfetamine (Adam and eve; *N*-ethyltenamfetamine; Eve; MDE; MDEA; 3,4-methylenedioxyethamfetamine)
- *N*-hydroxy methylenedioxyamfetamine (*N*-hydroxytenamfetamine *N*-hydroxy MDA; 3,4-methylenedioxy-*N*-hydroxyamfetamine)
- methoxyamfetamine (Death; 4-methoxyamfetamine; *p*-methoxyamfetamine; PMA)
- methylenedioxymethamfetamine (Ecstasy) (see p. 2325.2)
- 2,4,5-trimethoxyamfetamine (2,4,5-TMA; TMA; TMA-2)

In large doses the adverse effects of tenamfetamine and related compounds are similar to those of dexamfetamine and may be treated similarly (see p. 2319.2). Fatalities have been associated with the abuse of some of these compounds.

Reviews of the properties of some designer drugs, including phenylethylamine compounds.

1. Buchanan JF, Brown CR. Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; 3: 1–17.
2. Chesher G. Designer drugs—the "whats" and the "whys". *Med J Aust* 1990; 153: 157–61.
3. Christophersen AS. Amphetamine designer drugs—an overview and epidemiology. *Toxicol Lett* 2000; 112-113: 127–31.
4. Kraemer T, *et al.* Toxicokinetics of amphetamines: metabolism and toxicokinetic data of designer drugs, amphetamine, methamphetamine, and their N-alkyl derivatives. *Ther Drug Monit* 2002; 24: 277–89.
5. Reneman L. Designer drugs: how dangerous are they? *J Neural Transm* 2003; 66 (suppl): 61–83.

Tesofensine *(rINN)*

NS-2330; Tesofensina; Tésofensine; Tesofensinum; Тезофен-син.

(1*R*,2*R*,3*S*,5*S*)-3-(3,4-Dichlorophenyl)-2-(ethoxymethyl)-8-methyl-8-azabicyclo[3.2.1]octane.

$C_{17}H_{23}Cl_2NO$=328.3.

CAS — 195875-84-4.

UNII — 8LH9UKX9V1.

Profile

Tesofensine is a dopamine, noradrenaline and serotonin reuptake inhibitor that is being investigated for its use in the management of obesity.

References.

1. Astrup A, *et al.* Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372: 1906–13.

Thyroid and Antithyroid Drugs

The main role of the thyroid gland is to regulate tissue metabolism through production of the **thyroid hormones** 3,5,3',5'-tetra-iodo-L-thyronine (levothyroxine, L-thyroxine, thyroxine; T_4) and, in smaller amounts, 3,5,3'-tri-iodo-L-thyronine (liothyronine, L-tri-iodothyronine, tri-iodothyronine; T_3). Most of the T_3 in the body is derived from peripheral conversion of T_4.

The production of thyroid hormones is dependent on an adequate supply of dietary iodine. Iodine is reduced to iodide in the gastrointestinal tract and is then readily absorbed and actively transported into the thyroid, where it undergoes oxidation, catalysed by thyroid peroxidase. Oxidised iodide is incorporated into the glycoprotein thyroglobulin to form inactive iodotyrosines. A coupling reaction, also catalysed by thyroid peroxidase, yields the hormonally active iodothyronines, T_3 and T_4, joined by a peptide bond to thyroglobulin for storage in the follicular colloid. The release of proteolytic enzymes from lysosomes degrades the thyroglobulin into its constituent amino acids to release T_3 and T_4 into the circulation; iodide resulting from this reaction is recycled.

Thyroid hormone homoeostasis is maintained by autoregulatory mechanisms within the gland, and by the hypothalamic-pituitary-thyroid axis. In response to falling plasma concentrations of unbound T_3 and T_4, the hypothalamus secretes thyrotropin releasing hormone (protirelin; TRH—see p. 2344.2), which in turn stimulates the synthesis and release of thyroid stimulating hormone (thyrotropin; TSH—see p. 2346.1) by the anterior pituitary gland. TSH acts on its receptor in the thyroid gland to increase production of T_3 and T_4, and also to release hormone stored in the gland. As thyroid hormone concentrations in blood increase, the secretion of TSH, and possibly TRH, will be suppressed. The term euthyroidism is used when the thyroid gland is functioning normally and there are normal amounts of thyroid hormone in the blood.

Goitre and thyroid nodules

Goitre is the enlargement of the thyroid gland. The swelling may be focal (caused by a solitary thyroid nodule, adenoma, or cyst) or generalised, in which case it is usually diffuse at first, later becoming multinodular. The management of toxic (hormone oversecreting) goitres is discussed under Hyperthyroidism, below.

Non-toxic goitres may be associated with intrinsic defects in hormone production, or extrinsic factors such as dietary-iodine deficiency in endemic goitre (see Iodine Deficiency Disorders, p. 2337.3). Decreased secretion of thyroid hormone results in an excessive output of thyroid-stimulating hormone (TSH) from the pituitary. This stimulates thyroid-hormone production but also leads to hypertrophy and hyperplasia of the thyroid gland. If the response to TSH overcomes the deficiency in thyroid-hormone synthesis then the patient is goitrous and euthyroid but if the compensatory response to TSH is inadequate then goitre with hypothyroidism (see p. 2333.3) occurs. Other factors can also contribute, such as autoantibody-stimulated thyroid growth, and thyroid autonomy, in which the gland functions independently of TSH control.

The general aims in the management of thyroid masses are:

- the detection and treatment of malignancy
- the reduction of goitre or prevention of further enlargement, and the relief of obstructive symptoms
- the maintenance of a euthyroid state

In established **malignancy**, surgery, followed by levothyroxine replacement therapy, is the usual course (for further discussion of the treatment of thyroid cancer, see p. 716.1).

There is controversy as to whether a **benign solitary nodule** should be treated and, if so, how.[1] Surgery is sometimes indicated for symptomatic patients or for cosmetic reasons.[1-3] Laser ablation therapy is an alternative in those patients in whom surgery is not an option.[2] Alternatively suppressive therapy with doses of levothyroxine sufficient to suppress TSH production and reduce the size of the nodule has been widely practised.[1,3] However, treatment seems beneficial mostly in a subgroup of patients with small, solid nodules,[4] and guidelines[2,5] state that routine levothyroxine is not recommended; it may be considered for small nodules in young patients from areas of iodine deficiency, and in nodular goitres with no evidence of autonomous thyroid hormone production.[2] Sclerotherapy by percutaneous alcohol injection can produce substantial reductions, but the procedure is painful and requires considerable skill;[1,2] repeat injections are necessary to achieve complete cure.[3] Guidelines[2] consider it an option for cysts and complex nodules with a lot of fluid, but not for solid solitary nodules, whether hyperfunctioning or not. Radio-iodine (^{131}I) is an option for treatment of a functioning nodule.[1-3]

There is no ideal treatment for **benign multinodular goitre.**[6] Surgery is recommended for large goitres.[3,6] Non-surgical options include levothyroxine therapy and radio-iodine (^{131}I) therapy. Levothyroxine suppression therapy is effective in patients with **diffuse** non-toxic goitre, and may be of benefit in some patients with multinodular disease. However, many patients with large multinodular goitres have autonomous thyroid hormone production, and in such patients levothyroxine is of no benefit and may cause overt hyperthyroidism.[3] Radio-iodine (^{131}I) treatment appears to be more effective and better tolerated than levothyroxine,[7] and is the routine choice for non-toxic multinodular goitre in a few European countries.[3] However, in other countries with high dietary iodine intake, the uptake of iodine by the thyroid is low, and higher doses are necessary.[3] Thyrotropin alfa can increase the absorbed radio-iodine (^{131}I) dose, and this strategy is under investigation.[6]

1. Hegedüs L. The thyroid nodule. *N Engl J Med* 2004; 351: 1764–71.
2. Gharib H. *et al.* AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. *Endocr Pract* 2010; 16: 468–75. Full version: http://www.aace.com/sites/default/files/ThyroidGuidelines.pdf (accessed 18/05/11)
3. Hegedüs L. *et al.* Management of simple nodular goiter: current status and future perspectives. *Endocr Rev* 2003; 24: 102–32.
4. Castro MR. *et al.* Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: a meta-analysis. *J Clin Endocrinol Metab* 2002; 87: 4154–9.
5. Cooper DS. *et al.* The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer, November 2009. Available at: http://thyroidguidelines.net/sites/thyroidguidelines.net/files/file/ATA_DTC_Guidelines_2009.pdf (accessed 18/05/11)
6. Past S. *et al.* Time to reconsider nonsurgical therapy of benign non-toxic multinodular goitre: focus on recombinant human TSH augmented radioiodine therapy. *Eur J Endocrinol* 2009; 160: 517–28.
7. Wesche MFT. *et al.* A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. *J Clin Endocrinol Metab* 2001; 86: 998–1005.

Hyperthyroidism

Hyperthyroidism is overactivity of the thyroid gland, with consequent excess secretion of hormones. The terms thyrotoxicosis and hyperthyroidism are used interchangeably, although some apply 'thyrotoxicosis' to the *effects* of excessive thyroid hormone. The most common causes of hyperthyroidism are Graves' disease (diffuse toxic goitre) and hyperactivity arising from single or multiple thyroid nodules (toxic nodular goitre or Plummer's disease). Graves' disease (or Basedow's disease) is an auto-immune condition in which thyroid-stimulating antibodies bind to thyroid-stimulating hormone (TSH) receptors, mimicking the effect of prolonged TSH stimulation. Graves' disease, frequently occurs with other diseases such as Addison's disease, type 1 diabetes mellitus, and pernicious anaemia, and there may be a genetic predisposition. Iodine and its salts, or iodine-containing drugs such as amiodarone, can also be a cause of both hyperthyroidism and hypothyroidism (see Effects on Thyroid Function, under Amiodarone, p. 1302.3). Thyroiditis (an inflammation of the thyroid gland) may cause transient hyperthyroidism, followed by progression to hypothyroidism.

A **diagnosis** of primary hyperthyroidism may be confirmed by finding a low TSH value and a high concentration of free T_4 or T_3 in the circulation. Determination of TSH, which is low in hyperthyroidism due to negative feedback, allows differential diagnosis of hyperthyroidism from a TSH-secreting pituitary tumour.

Subclinical hyperthyroidism is characterised by normal thyroid hormone concentrations, decreased TSH concentrations, but no clinical symptoms. It has been reported to occur less frequently than subclinical hypothyroidism. Consensus on management has been lacking.[1-3] Treatment decisions are based on age, TSH concentrations, risk of progression to overt disease, symptoms, and cardiac and skeletal manifestations.[4] Generally, evidence supports treatment in patients with a TSH less than 0.1 milli-units/litre, in those with multinodular goitre, those with osteoporosis or at risk of atrial fibrillation.[1,3-6] Treatment options include antithyroid drugs and radio-active iodine (see below for discussions of both therapies);[3,4] partial thyroidectomy is reserved for those patients with multinodular goitre causing compression.[4]

There are three main forms of **treatment** for hyperthyroidism: drug therapy, use of radio-iodine, or surgery.

Drug therapy. The main **antithyroid drugs** are carbimazole (in the UK), thiamazole (in the USA), and propylthiouracil.[3,6-8] These are all thiourea drugs that inhibit thyroid hormone production; propylthiouracil also blocks peripheral conversion of thyroxine to tri-iodothyronine.[6,8] Carbimazole or thiamazole are preferred in most situations, particularly because of concerns about the hepatotoxicity of propylthiouracil (see Hyperthyroidism, under Propylthiouracil, p. 2344.1).

Many patients begin treatment with an antithyroid drug in the hope of achieving remission (defined as euthyroidism for 1 year after stopping drug therapy);[7-10] they receive higher doses initially until they become euthyroid, generally within 1 to 2 months. Once a response to the antithyroid drug has been obtained, patients with more severe or recurrent disease may require ablative treatment with either radio-iodine or surgery (see below), while those with mild to moderate disease may be best managed with lower maintenance doses of antithyroid drugs (*'titration regimen'*). Treatment is typically given for 12 to 18 months.[3,6,7,9,11-13] Relapse at some stage after stopping therapy occurs in about 50 to 60% of cases,[7,10,11] usually within 3 to 6 months after stopping the drugs,[7] but may also occur years later.[8] Use of levothyroxine during and after antithyroid therapy was reported to reduce relapse rates, but subsequent studies failed to corroborate this,[7] and concomitant[8,11] or continued[13] thyroxine replacement therapy is considered to provide no benefit in terms of recurrence.

The *'block-replace regimen'* has also been used, in which thyroxine replacement therapy is added, while maintaining the high initial dose of antithyroid drug.[9] This has been suggested to help prevent hypothyroidism induced by the antithyroid drug,[8] and some consider it useful for patients with unstable hyperthyroidism.[11] Therapy is usually given for 6 to 12 months,[8] although 6 months was found to be as effective as 12 months in one study.[13] However, the titration regimen was found to be no less effective than the block-replace regimen, with fewer adverse effects and fewer patient withdrawals,[13] and US guidelines recommend against using the block-replace regimen.[3]

Beta blockers are used to relieve symptoms of hyperthyroidism such as tachycardia, tremor, anxiety, and sweating.[6,8,10] They are used as short-term adjuncts to therapy.[3,6,8,10] Their use in heart failure associated with thyrotoxicosis is controversial due to the risk of cardiac deterioration.[14] In general, all beta blockers are considered equally effective, although those with a longer duration of action such as atenolol, metoprolol, or nadolol are preferred.[8] Those who cannot tolerate beta blockers may be treated with calcium-channel blockers.[3]

Potassium and sodium perchlorate have also been used; they increase responsiveness to conventional antithyroid drugs and may be useful in patients with iodine-induced hyperthyroidism, possibly including that associated with amiodarone therapy, as well as for prophylaxis against hyperthyroidism from the use of iodinated contrast agents.[15]

In those patients in whom drug therapy fails to achieve long-term remission, ablative therapy may be considered in the form of radio-iodine therapy or surgery.

Radio-iodine therapy with ^{131}I as oral sodium iodide (^{131}I) treats hyperthyroidism by destroying the functioning cells of the thyroid gland to produce a state of mild hypothyroidism.[3] It is often used as initial therapy in the USA.[3,8] It is also used in patients who have not responded to antithyroid drug therapy or who have relapsed after it.[3,7,8,11]

Pretreatment of patients with an antithyroid drug for 4 to 8 weeks before radio-iodine therapy has been advocated, to deplete the thyroid gland of stored hormone and reduce the risk of precipitating thyroid storm due to ^{131}I-induced thyroiditis. However, this is not considered necessary for all patients, although it is generally agreed that the elderly or those with severe disease or increased risk of cardiac symptoms should receive some form of pretreatment.[3,8,16] Meta-analysis has shown that use of antithyroid drugs in the week before or after radio-iodine therapy decreases its effectiveness, increasing the risk of treatment failure.[17] The efficacy of radio-iodine treatment is not diminished after treatment with carbimazole or thiamazole as long as the drug is stopped 3 to 5 days before radio-iodine is given;[6] US guidelines[3] recommend that if thiamazole pretreatment is used, the drug should be stopped 3 to 5 days before radio-

iodine is given and restarted 3 to 7 days later before being tapered off over 4 to 6 weeks as thyroid function normalises. Although it has been considered that a poor response to radio-iodine was more likely with propylthiouracil than thiamazole,[6-8] this was not supported by meta-analysis.[17] Pretreatment with a beta blocker for symptomatic relief may be given to patients receiving radio-iodine,[18] and US guidelines[3] recommend this in patients with severe disease or at increased risk from worsening symptoms.

The dose of radio-iodine needed to achieve control is difficult to predict and there has been disagreement on the most appropriate dosage schedule.[18] A radioactive iodine uptake test can be used to help estimate the thyroid's ability to trap iodine, but giving a fixed dose (typically 10 to 15 millicuries) may be just as effective.[3] Radio-iodine therapy may take several months to achieve a clinical response, and cover with an antithyroid drug may be required during this period.[11] Radio-iodine is not generally considered to increase the risk of malignancy,[3,8,11] teratogenicity,[11,16] or infertility,[3,8] but it is contra-indicated in pregnancy and while breast feeding.[3,6] Adequate radio-iodine therapy generally results in hypothyroidism and all patients require long-term follow-up and possible levothyroxine replacement therapy.[3] Cohort studies have found increased mortality in those patients with hyperthyroidism treated with radio-iodine.[19,20] However, this risk was no longer evident once patients with overt hypothyroidism (induced by radio-iodine therapy) were given thyroxine replacement therapy. The authors considered these findings to strongly support a definitive treatment of hyperthyroidism with doses of radio-iodine sufficient to cause overt hypothyroidism, and the prompt treatment of subclinical hypothyroidism after radio-iodine therapy.[20]

Surgery. Thyroidectomy is usually used only in specific situations. These include patient preference, pregnancy, patients who are intolerant of or unresponsive to antithyroid drugs, the presence of a very large goitre, or suspicious nodules.[3,8,10] Total thyroidectomy is the procedure of choice, to prevent recurrent hyperthyroidism.[3,8,11] Complications may include hypoparathyroidism and laryngeal nerve injury.[3,6,8] Euthyroidism is established before surgery with antithyroid drugs if possible,[3,6,11] and iodide is given for 7 to 10 days before surgery to reduce the vasculature of the gland.[3,6,10] Alternatively, a combination of iodine and a beta blocker,[3] and possibly glucocorticoids,[8] has been suggested if surgery is urgent. Iopanoic acid has been used short-term for rapid preparation for surgery, but is ineffective as long-term therapy.[6] However, some[21] have stated that pre-operative iodine probably has no beneficial effect. Surgery results in permanent hypothyroidism in most patients,[6] necessitating thyroxine replacement therapy.[3,11]

Arterial embolisation. There are some patients who cannot, or choose not to, receive any of the three main forms of treatment for hyperthyroidism. Thyroid arterial embolisation has been used as an alternative with an outcome similar to that of subtotal thyroidectomy.[22]

If untreated or inadequately controlled, hyperthyroidism can complicate **pregnancy** and have adverse perinatal effects.[23-25] While there is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcome,[23] and treatment is therefore considered unnecessary,[24] overt hyperthyroidism is generally treated throughout pregnancy with an antithyroid drug at the minimum dose needed to maintain a borderline euthyroid state.[3,7,8] Propylthiouracil has usually been considered the treatment of choice, mainly because of reports of congenital defects with alternatives.[7,10,23-25] If propylthiouracil is unavailable or unsuitable for use carbimazole and thiamazole are recommended;[7,23] the potential maternal and fetal risk of not treating active hyperthyroidism is considered to outweigh the risk of rare congenital abnormalities.[25] Propylthiouracil is itself associated with a risk of maternal and neonatal hepatotoxicity, and US guidelines recommend that its use should be limited to the first trimester, and that an alternative antithyroid drug, such as thiamazole, should be considered for treatment later in pregnancy.[3] Occasionally, the antithyroid drug can be withdrawn in the third trimester.[7,8] Drug therapy during pregnancy may cause fetal or neonatal hypothyroidism, with or without goitre. This risk appears unrelated to the dose of the drug,[25,26] and the condition may mask neonatal hyperthyroidism[26] (see below). While a beta blocker such as propranolol may be used short-term as adjunctive therapy during pregnancy,[24,25] the use of radio-iodine is contra-indicated during pregnancy and breast feeding.[3,8,23-25] The block-replace regimen is also contra-indicated during pregnancy, because the dose of antithyroid drug that crosses the placenta may be excessive in proportion to the amount of levothyroxine, which increases the risk of fetal goitre and hypothyroidism.[24,25]

For pregnant women who have severe refractory hyperthyroidism, or who cannot take drug therapy for any reason, surgery may be needed. If it cannot be delayed till after birth, it is best done during the second trimester.[3,23,24]

Fetal or neonatal hyperthyroidism may occur rarely due to transfer of thyroid-stimulating immunoglobulins across the placenta.[26-28] These immunoglobulins may be present even in women who have been receiving levothyroxine for some years after thyroidectomy or radio-iodine treatment. Fetal disease can also be caused by insufficient treatment for maternal hyperthyroidism.[28] Fetal hyperthyroidism may be treated by giving antithyroid drugs to the mother (which can lead to maternal hypothyroidism);[28] neonatal disease is treated with antithyroid drugs, iodide, and appropriate therapy for cardiovascular complications.[27]

Treatment options for **children** with hyperthyroidism are the same as for adults, namely antithyroid drugs, surgery, or radio-iodine;[3,29-31] the initial choice of therapy varies between countries.[30] Because a minority of children will go into remission with antithyroid drug therapy, treatment with thiamazole for 1 to 2 years is noted as a potential first-line treatment for most children by US guidelines.[3] However, short- and long-term effects of drug therapy can be a cause for concern,[29,31] and some consider definitive therapy in the form of surgery or radio-iodine to be unavoidable.[29] There is some controversy as to the optimal dose of radio-iodine; limited data suggest that a gland-specific low dose is potentially effective for paediatric disease,[30] while others consider a low dose to be associated with an increased risk of malignancy, and advocate higher doses.[31] Radio-iodine is usually considered best avoided in children under 5 years of age.[3,31]

Thyroid storm (also known as thyroid crisis or thyrotoxic crisis) is an extreme accentuation of the hyperthyroid state and should be treated as a medical emergency. It usually occurs in patients with Graves' disease, but can also occur in other types of hyperthyroidism. It is usually abrupt in onset and is often related to some precipitating factor such as inadequate preparation for thyroidectomy or radio-iodine therapy, or infection in previously unrecognised hyperthyroid subjects. Treatment consists of supportive measures, treatment of the precipitating cause, and drug therapy to halt the synthesis, release, and peripheral effects of thyroid hormone.[3,32] The order of therapy is important; inhibition of thyroid gland synthesis with an antithyroid drug should be started before iodine is given to inhibit release of stored thyroid hormone from the gland, to avoid the stimulation of synthesis that could occur if iodine were given first. However, there is some controversy as to the appropriate delay; 30 to 60 minutes is advocated, depending on the clinical urgency.[32] Therapy to decrease peripheral effects includes beta blockers and corticosteroids. Lithium may be used when antithyroid drugs are contra-indicated; it can also be used with antithyroid drugs.[32]

The clinical manifestations of **Graves' ophthalmopathy** may not always occur with those of systemic hyperthyroidism, and may also occur in patients who are euthyroid or even hypothyroid;[33-35] immunoreactivity against the thyrotropin receptor may underlie the disease.[33] Severity is classified as mild, moderate, or severe based on the degree of proptosis, constancy of diplopia, and the effect of optic neuropathy on visual acuity.[36] Treatment aims to protect vision, relieve discomfort, correct dysfunction, and improve cosmetic deformity.[33] Factors such as cigarette smoking that are associated with an increased risk of progression should be eliminated or controlled; thyroid dysfunction should be corrected.[3,34,36] Most patients with mild ocular involvement in hyperthyroidism require no specific therapy;[34,36] dry eye should be managed appropriately (see p. 2190.1). Corticosteroids are often used for moderate to severe disease;[34,36] intravenous pulse therapy has been shown to have a small but statistically significant advantage over oral therapy.[37] However, the optimal glucocorticoid regimen remains uncertain.[34] Orbital corticosteroid injections have been used with varying levels of success.[36] Orbital radiotherapy remains a standard treatment option, despite disputes as to its efficacy,[36,37] and the combination of this and oral glucocorticoids has been shown to be synergistic.[34,37] The appropriate use of radio-iodine therapy for managing hyperthyroidism in patients with Graves' ophthalmopathy remains uncertain[34] as it has been reported to exacerbate ophthalmopathy in some patients. US guidelines[3] suggest that in patients with moderate to severe disease thiamazole or surgery should be preferred; in milder disease radio-iodine is an option but concurrent corticosteroid treatment should be considered unless ophthalmopathy is inactive. Corticosteroids were definitely recommended when radio-iodine was given to those with risk factors such as smoking. Other drugs that have been investigated include immunosuppressive agents and somatostatin analogues.[34,36,37] Ciclosporin plus prednisone has been reported to be of benefit,[33,36] and methotrexate may be an option for refractory disease.[36] Somatostatin analogues such as long-acting octreotide and lanreotide have marginal clinical efficacy.[37]

Surgical orbital decompression may be required if patients do not respond to such therapy or cannot tolerate its adverse effects, or if vision is threatened by severe optic nerve compression.[34,36]

Beta blockers may be used as primary treatment in patients with thyrotoxicosis due to **thyroiditis**, in whom thiourea antithyroid drugs are inappropriate.[3,6] NSAIDs, or in those with more severe symptoms or who fail to respond, corticosteroids, are also recommended in patients with symptomatic subacute thyroiditis.[3]

1. Papi G, *et al.* A clinical and therapeutic approach to thyrotoxicosis with thyroid-stimulating hormone suppression only. *Am J Med* 2005; 118: 349–61.
2. Gharib H, *et al.* Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *J Clin Endocrinol Metab* 2005; 90: 581–5. Also available at: http://jcem.endojournals.org/cgi/reprint/90/1/581.pdf (accessed 19/05/11)
3. Bahn RS, *et al.* Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid* 2011; 21: 593–646. Also printed in *Endocr Pract* 2011; 17: 456–520. Also available at: https://www.aace.com/sites/default/files/HyperGuidelines2011.pdf (accessed 28/06/11)
4. Jones DD, *et al.* Subclinical thyroid disease. *Am J Med* 2010; 123: 502–4.
5. Surks MI, *et al.* Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; 291: 228–38.
6. Pearce EN. Diagnosis and management of thyrotoxicosis. *BMJ* 2006; 332: 1369–73.
7. Cooper DS. Antithyroid drugs. *N Engl J Med* 2005; 352: 905–17.
8. Cooper DS. Hyperthyroidism. *Lancet* 2003; 362: 459–68.
9. Kharlip J, Cooper DS. Recent developments in hyperthyroidism. *Lancet* 2009; 373: 1930–2.
10. Brent GA. Graves' disease. *N Engl J Med* 2008; 358: 2594–2605.
11. Topliss DJ, Eastman CJ. Diagnosis and management of hyperthyroidism and hypothyroidism. *Med J Aust* 2004; 180: 186–93.
12. Cooper DS. Antithyroid drugs in the management of patients with Graves' disease: an evidence-based approach to therapeutic controversies. *J Clin Endocrinol Metab* 2003; 88: 3474–81.
13. Abraham P, *et al.* Antithyroid drug regimen for treating Graves' hyperthyroidism. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 19/05/11).
14. Ko GTC, *et al.* Should β-blocking agents be used in thyrotoxic heart disease? *Med J Aust* 1995; 162: 426–7.
15. Leung AM, *et al.* Perchlorate, iodine and the thyroid. *Best Pract Res Clin Endocrinol Metab* 2010; 24: 133–41.
16. Weetman AP. Graves' disease. *N Engl J Med* 2000; 343: 1236–48.
17. Walter MA, *et al.* Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2007; 334: 514–17.
18. Kaplan MM, *et al.* Treatment of hyperthyroidism with radioactive iodine. *Endocrinol Metab Clin North Am* 1998; 27: 205–23.
19. Franklyn JA, *et al.* Mortality after the treatment of hyperthyroidism with radioactive iodine. *N Engl J Med* 1998; 338: 712–18.
20. Franklyn JA, *et al.* Thyroid function and mortality in patients treated for hyperthyroidism. *JAMA* 2005; 294: 71–80.
21. Vanderpump MPJ, *et al.* Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. *BMJ* 1996; 313: 539–44.
22. Xiao H, *et al.* Arterial embolization: a novel approach to thyroid ablative therapy for Graves' disease. *J Clin Endocrinol Metab* 2002; 87: 3583–9.
23. Abalovich M, *et al.* Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2007; 92 (suppl): S1–S47. Also published in: *Thyroid* 2007; 17: 1159–67. Also available at: http://www.endo-society.org/guidelines/final/upload/Clinical-Guideline-Management-of-Thyroid-Dysfunction-during-Pregnancy-Postpartum.pdf (accessed 29/12/08)
24. Fitzpatrick DL, Russell MA. Diagnosis and management of thyroid disease in pregnancy. *Obstet Gynecol Clin North Am* 2010; 37: 173–93.
25. Marx H, *et al.* Hyperthyroidism and pregnancy. *BMJ* 2008; 336: 663–7.
26. Girling JC. Thyroid disease in pregnancy. *Hosp Med* 2000; 61: 834–40.
27. Ogilvy-Stuart AL. Neonatal thyroid disorders. *Arch Dis Child Fetal Neonatal Ed* 2002; 87: F165–F171.
28. Polak M, Van Vliet G. Therapeutic approach of fetal thyroid disorders. *Horm Res Paediatr* 2010; 74: 1–5.
29. Rivkees SA. The treatment of Graves' disease in children. *J Pediatr Endocrinol Metab* 2006; 19: 1095–1111.
30. Ma C, *et al.* Radioiodine treatment for pediatric Graves' disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 19/05/11).
31. Rivkees SA, Dinauer C. An optimal treatment for pediatric Graves' disease is radioiodine. *J Clin Endocrinol Metab* 2007; 92: 797–800.
32. Nayak B, Burman K. Thyrotoxicosis and thyroid storm. *Endocrinol Metab Clin North Am* 2006; 35: 663–86.
33. Hart RH, Perros P. Glucocorticoids in the medical management of Graves' ophthalmopathy. *Minerva Endocrinol* 2003; 28: 223–31.
34. Bartalena L, Tanda ML. Graves' ophthalmopathy. *N Engl J Med* 2009; 360: 994–1001.
35. Bahn RS. Graves' ophthalmopathy. *N Engl J Med* 2010; 362: 726–38.
36. Modjtahedi SP, *et al.* Pharmacological treatments for thyroid eye disease. *Drugs* 2006; 66: 1685–1700.
37. Stiebel-Kalish H, *et al.* Treatment modalities for Graves' ophthalmopathy: systematic review and metaanalysis. *J Clin Endocrinol Metab* 2009; 94: 2708–16.

Hypothyroidism

Hypothyroidism is the clinical syndrome resulting from deficiency of thyroid hormones. The term **myxoedema** is often reserved for severe or advanced hypothyroidism. Hypothyroidism is usually primary, resulting from malfunction of the thyroid gland. In areas where iodine intake is sufficient the commonest cause of hypothyroidism is auto-immune lymphocytic thyroiditis of which there are two major variants. In **Hashimoto's thyroiditis** there is also goitre whereas in **idiopathic** or **primary myxoedema (atrophic thyroiditis)** there is no thyroid enlargement. High-dose radiotherapy to the head and neck, radio-iodine thyroid ablation, or thyroidectomy can also cause hypothyroidism. Hypothyroidism can also be caused by a deficiency of iodine. Endemic cretinism is a result of

maternal, and hence fetal, iodine deficiency and consequent lack of thyroid hormone production (see Iodine Deficiency Disorders, p. 2337.3). Iodine and its salts, or iodine-containing drugs such as amiodarone, can also be a cause of both hypothyroidism or hyperthyroidism (see Effects on Thyroid Function, under Amiodarone, p. 1302.3). Drugs that decrease thyroid hormone synthesis, such as lithium, can also be a cause of hypothyroidism. Central hypothyroidism occurs secondary to disorders of the hypothalamus or pituitary gland.

The **diagnosis** of hypothyroidism may be confirmed by a raised thyroid stimulating hormone (TSH) value and a low free T_4 or T_3 concentration in the circulation. Protirelin and thyrotrophin have also been used for the differential diagnosis of hypothyroidism.

Subclinical hypothyroidism is a condition in which there are normal concentrations of thyroid hormones, raised concentrations of TSH, but no clinical symptoms. Patients with subclinical hypothyroidism are at a greater risk of developing clinical hypothyroidism if they have higher TSH concentrations, or if antibodies against thyroid peroxidase are present.[1-3] Controversy has surrounded the issue of whether the consequences of undiagnosed, and therefore untreated, subclinical disease justifies widespread routine screening; screening has been proposed in those with several risk factors, and for pregnant women.[4,5] Management differs depending on TSH concentrations. While levothyroxine therapy is generally recommended if TSH concentrations are greater than 10 milliunits/litre,[1-9] treatment in those with concentrations below this remains a subject of much debate. Arguments for treatment include avoiding progression to overt disease, improvement in symptoms and quality of life, improvement in lipid profiles, and the possible reduction in cardiovascular risk factors.[4,9,10] Arguments against include the danger of overtreatment, leading to hyperthyroidism,[5] and the fact that, while studies have shown an association between subclinical hypothyroidism and cardiovascular morbidity and mortality,[3] evidence is strongest in those with TSH greater than 10 milliunits/litre.[7,11] Furthermore, while some studies have shown improvement in cardiovascular risk factors with levothyroxine therapy,[12] and there is some evidence that it improved lipid profiles and left ventricular function,[13] others have failed to show conclusive benefit of thyroxine replacement in reducing adverse cardiovascular outcomes,[3,13] especially in those with TSH concentrations between 5 to 10 milliunits/litre.[7] It has been recommended that therapy be individualised in these patients, taking into account patient preference, presence of symptoms, age, and associated comorbidities.[9] Levothyroxine treatment has also been recommended if TSH levels are between 5 and 10 milliunits/litre and the patient has symptoms of hypothyroidism,[3,5-7] or goitre,[1,7,8] or dyslipidaemia,[2,7,8] or if thyroid antibodies are present.[1,2,7,8,14] Treatment is also generally recommended for pregnant women,[3,6,8,9,13,15] infants,[16] and children with subclinical hypothyroidism.[9]

Hypothyroidism is readily **treated** by lifelong replacement therapy with levothyroxine.[1-3,7,10,14,17] Initial and periodic checks should be made to ensure that thyroid replacement treatment is restoring deficiencies in thyroid hormone but not providing an excess. This is best done by monitoring hormone concentrations and the goal of replacement therapy is a normal TSH value.[1,7,14,17,18] The dose of levothyroxine needed to normalise TSH may be supraphysiological, resulting in a slightly elevated T_4 value.[18] Although the thyroid gland produces both T_3 (liothyronine) and T_4 (thyroxine), T_3 is mainly produced by peripheral monodeiodination of circulating T_4 and it is therefore sufficient to give levothyroxine alone. There is no rationale for the use of combined preparations containing liothyronine and levothyroxine,[2,3,7,14,17,18] or of dried thyroid hormone extracts,[3] which may lead to elevated serum concentrations of T_3 and thyrotoxic symptoms.[7,10,14] Nonetheless, some patients prefer a combination and some clinicians recommend combination therapy when a patient remains lethargic or has memory impairment despite a normalised TSH with levothyroxine therapy.[18] Liothyronine itself may be used initially for its rapid onset of action in severe hypothyroid states such as myxoedema coma (see below).

Untreated or inadequately controlled hypothyroidism during **pregnancy** increases the risk of early and late obstetric complications and can have potentially serious adverse effects on the mother and the fetus, including impaired cognitive development in the latter.[1,15,17,19-21] Levothyroxine therapy of clinical hypothyroidism during pregnancy is standard practice.[1,15] During the first trimester there is an estimated 30 to 50% increase in the patient's levothyroxine requirement,[21,22] and some have suggested that hypothyroid women should increase their dose by 30% as soon as they discover they are pregnant.[17,19-21] A prospective study of dosage increases, started at confirmation of pregnancy in hypothyroid women, provided evidence that a roughly 30% increase in maternal levothyroxine (accomplished by the addition of 2 tablets weekly) significantly reduced the risk of maternal hypothyroidism throughout the first trimester.[23] Thyroid function tests should be performed as soon as pregnancy is confirmed,[17] and every 2 to 6 weeks thereafter;[1,17,20,22] the TSH concentration is used to guide further levothyroxine dose adjustment.[14,17,20] Some suggest that once the patient is stable, TSH can be checked every 8 weeks.[21]

Congenital or neonatal hypothyroidism is defined as thyroid hormone deficiency at birth.[16] Unrecognised, it can lead to mental retardation, and newborn screening programmes are standard in many countries.[16,24,25] The timing of therapy and the severity of hypothyroidism are important factors in determining the neurocognitive outcome.[16] All infants should be rendered euthyroid as promptly as possible, and rapid replacement therapy with adequate doses of levothyroxine is the treatment of choice;[16,24,25] clinical evaluation should be performed every few months during the first 3 years of life.[16,24] In those with more severe hypothyroidism at diagnosis, some small degree of deficit and incoordination may remain;[16,24,26] tailoring the initial levothyroxine dose to the severity of hypothyroidism and giving higher doses of levothyroxine has been advocated.[16] However, a systematic review[27] failed to confirm the benefits of a high initial dose over a low dose, due to paucity of data, and further studies are required.

Childhood (acquired) hypothyroidism occurs after 6 months of age: if the onset is after 2 to 3 years of age, no permanent intellectual damage or neurological deficit is considered likely. Treatment is with levothyroxine, and doses are individualised according to serum TSH and free T_4 concentrations. Overall, the prognosis is good if it is diagnosed early and the hypothyroidism is not of long-standing duration.[28]

Myxoedema coma (or hypothyroid coma) is an extreme accentuation of the hypothyroid state and should be treated as a medical emergency. It typically presents in older women in the winter months, and is often related to some precipitating factor such as drug therapy, systemic illness, or other causes. It has a poor prognosis, and despite treatment, is associated with substantial mortality.[7,10,17,29,30] Treatment consists of supportive measures aimed at cardiovascular, respiratory, and neurological symptoms, the management of any precipitating factor or coexisting problems, and thyroid hormone replacement therapy.[7,17,29,30] Treatment should include intravenous hydrocortisone because of the likelihood of adrenocortical insufficiency;[17,29,30] the first dose of this should be given before thyroid hormone therapy,[17] and then tapered and stopped on the basis of clinical response.[29] Controversy exists as to which preparation of thyroid hormone should be used, and the optimal dose and regimen. Proponents variously advocate the use of levothyroxine alone, or liothyronine alone, or a combination of both.[7,14,17,29,30] Advantages of liothyronine include its rapid onset of action, the fact that it crosses the blood-brain barrier more readily than levothyroxine, and lack of any need for peripheral conversion of T_4 to T_3, which may be compromised in sick hypothyroid patients.[17,29] However, results with liothyronine monotherapy have been mixed, with some fatalities. There may be an increased risk of cardiac complications,[30] and serum concentrations fluctuate.[29] Patient selection and the choice of dose regimen may be as important as which drug is used.[30] Intravenous therapy should be used initially until oral therapy is possible.[17,29,30] Alternatively, the nasogastric route may be used.[29]

1. AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract* 2002; 8: 457–69. Amended 2006 version available at: http://www.aace.com/sites/default/files/hypo_hyper.pdf (accessed 19/05/11)
2. Topliss DJ, Eastman CJ. Diagnosis and management of hyperthyroidism and hypothyroidism. *Med J Aust* 2004; 180: 186–93.
3. Vaidya B, Pearce SHS. Management of hypothyroidism in adults. *BMJ* 2008; 337: a801.
4. Gharib H, *et al.* Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *J Clin Endocrinol Metab* 2005; 90: 581–5. Also available at: http://jcem.endojournals.org/cgi/reprint/90/1/581.pdf (accessed 19/05/11)
5. Arrigo T, *et al.* Subclinical hypothyroidism: the state of the art. *J Endocrinol Invest* 2008; 31: 79–84.
6. Surks MI, *et al.* Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; 291: 228–38.
7. McDermott MT. Hypothyroidism. *Ann Intern Med* 2009; 151: ITC6-1–ITC6-14.
8. Jones DD, *et al.* Subclinical thyroid disease. *Am J Med* 2010; 123: 502–4.
9. Patourechi V. Subclinical hypothyroidism: an update for primary care physicians. *Mayo Clin Proc* 2009; 84: 65–71.
10. Roberts CGP, Ladenson PW. Hypothyroidism. *Lancet* 2004; 363: 793–803.
11. Rodondi N, *et al.* Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010; 304: 1365–74.
12. Razvi S, *et al.* The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 2007; 92: 1715–23.
13. Villar HCCE, *et al.* Thyroid hormone replacement for subclinical hypothyroidism. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley: 2007 (accessed 27/05/11).
14. Singer PA, *et al.* American Thyroid Association. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Available at: http://thyroidguidelines.net/hypothyroidism_1995/guidelines (accessed 29/06/11)
15. Reid SM, *et al.* Interventions for clinical and subclinical hypothyroidism in pregnancy. Available in The Cochrane Database of Systematic Reviews: Issue 7. Chichester: John Wiley; 2010 (accessed 27/05/11).
16. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. *Orphanet J Rare Dis* 2010; 5: 17.
17. Devdhar M, *et al.* Hypothyroidism. *Endocrinol Metab Clin North Am* 2007; 36: 595–615.
18. Joffe RT, *et al.* Treatment of clinical hypothyroidism with thyroxine and triiodothyronine: a literature review and metaanalysis. *Psychosomatics* 2007; 48: 379–84.
19. Alexander EK, *et al.* Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004; 351: 241–9.
20. Glinoer D, Abalovich M. Unresolved questions in managing hypothyroidism during pregnancy. *BMJ* 2007; 335: 300–302.
21. Fitzpatrick DL, Russell MA. Diagnosis and management of thyroid disease in pregnancy. *Obstet Gynecol Clin North Am* 2010; 37: 173–93.
22. Abalovich M, *et al.* Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2007; 92 (suppl): S1–S47. Also published in: *Thyroid* 2007; 17: 1159–67. Also available at: http://www.endo-society.org/guidelines/final/upload/Clinical-Guideline-Management-of-Thyroid-Dysfunction-during-Pregnancy-Postpartum.pdf (accessed 29/12/08)
23. Yassa L, *et al.* Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. *J Clin Endocrinol Metab* 2010; 95: 3234–41.
24. Rose SR, *et al.* American Academy of Pediatrics. American Thyroid Association. Lawson Wilkins Pediatric Endocrine Society. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics* 2006; 117: 2290–2303. [Re-affirmed December 2011] Available at: http://pediatrics.aappublications.org/cgi/reprint/117/6/2290 (accessed 11/05/12)
25. Hopwood NJ. Treatment of the infant with congenital hypothyroidism. *J Pediatr* 2002; 141: 752–4.
26. Rovet JF. Congenital hypothyroidism: long term outcome. *Thyroid* 1999; 9: 741–8.
27. Ng SM, *et al.* High versus low dose of initial thyroid hormone replacement for congenital hypothyroidism. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2009 (accessed 26/05/11).
28. Counts D, Varma SK. Hypothyroidism in children. *Pediatr Rev* 2009; 30: 251–8.
29. Wartofsky L. Myxedema coma. *Endocrinol Metab Clin North Am* 2006; 35: 687–98.
30. Kwaku MP, Burman KD. Myxedema coma. *J Intensive Care Med* 2007; 22: 224–31.

Benzylthiouracil

Benciltiouracilo; Бензилтиоурацил.

6-Benzyl-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one; 6-Benzyl-2-mercaptopyrimidin-4-ol; 6-Benzyl-2-thiouracil.

$C_{11}H_{10}N_2OS$=218.3

CAS — 33086-27-0; 6336-50-1.

ATC — H03BA03.

ATC Vet — QH03BA03.

UNII — PZ35LUM333.

Profile

Benzylthiouracil is a thiourea antithyroid drug similar to carbimazole (below). It is given in the treatment of hyperthyroidism (p. 2332.2) in an initial oral dose of 150 to 200 mg daily, reducing gradually to a maintenance dose of 100 mg daily; it is given in divided doses, preferably with food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Basdene.

Carbimazole *(BAN, rINN)*

Carbimazol; Carbimazolum; Karbimatsoli; Karbimazol; Karbimazolas; Карбимазол.

Ethyl 3-methyl-2-thioxo-4-imidazoline-1-carboxylate.

$C_7H_{10}N_2O_2S$=186.2

CAS — 22232-54-8.

ATC — H03BB01.

ATC Vet — QH03BB01.

UNII — 8KQ660G60G.

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

Ph. Eur. 8: (Carbimazole). A white or yellowish-white crystalline powder. Slightly soluble in water; soluble in alcohol and in acetone.

Uses and Administration

Carbimazole is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p. 2332.1). It is used in the management of hyperthyroidism (p. 2332.2), including the treatment of Graves' disease, the preparation of hyperthyroid patients for thyroidectomy, as an adjunct to radio-iodine therapy, and in the treatment of thyroid storm.

Carbimazole is completely metabolised to thiamazole and it is this metabolite that is responsible for the antithyroid activity of carbimazole.

Carbimazole is given orally in a typical initial dosage of 15 to 40 mg daily, in divided doses; occasionally up to 60 mg daily may be required. Control of symptoms is usually achieved in 1 to 2 months. When the patient is euthyroid the dose is gradually reduced to the smallest amount that will maintain the euthyroid state. Typical maintenance doses are 5 to 15 mg daily, which may be given as a single daily dose. Higher initial doses may be needed in thyroid storm.

Carbimazole is also given orally in a dose of 20 to 60 mg daily, with supplemental levothyroxine, as a *blocking-replacement regimen.*

Either form of maintenance treatment is usually continued for at least a year, and often for 18 months; up to 2 years of treatment may be required.

For the use of carbimazole in children and adolescents, see below.

Administration in children. For the treatment of hyperthyroidism (including Graves' disease) in neonates and children up to 12 years of age, the *BNFC* recommends an initial oral dose of carbimazole 750 micrograms/kg (up to a maximum of 30 mg) daily, in divided doses or as a single dose. Children aged 12 to 18 years may be given 30 mg daily initially, in single or divided doses. Doses are adjusted according to response; higher initial doses may be needed in thyroid storm.

Adverse Effects, Treatment, and Precautions

Adverse effects from carbimazole and other thiourea antithyroid drugs occur most frequently during the first 8 weeks of treatment. An immune mechanism has been implicated in many of these reactions and cross-sensitivity between the thiourea antithyroid drugs may occur.

The most common minor adverse effects are nausea and vomiting, gastric discomfort, headache, arthralgia, rashes, and pruritus. These effects are usually self-limiting and may not require therapy to be stopped. However, propylthiouracil should be stopped if arthralgia occurs, as severe transient migratory polyarthritis may develop. Similarly, urticaria with propylthiouracil may herald a serious hypersensitivity reaction and the drug should be stopped; cross-sensitivity for this adverse effect is uncommon and an alternative thiourea drug may be tried.

Bone marrow depression including neutropenia, leucopenia, eosinophilia, and agranulocytosis has been reported. Agranulocytosis is the most serious adverse effect associated with this class of drugs, and fatalities have occurred. Patients or their carers should be told how to recognise such toxicity and should be advised to seek immediate medical attention if mouth ulcers or sore throat, fever, bruising, malaise, or non-specific illness develop. Full blood counts should be performed, and treatment should be stopped immediately if there is any clinical or laboratory evidence of neutropenia. Aplastic anaemia or isolated thrombocytopenia have been reported rarely, as have haemolytic anaemia and hypoprothrombinaemia.

Hepatotoxicity can occur with the thiourea drugs, and can be serious. Jaundice is the most common presentation with carbimazole; there have been rare reports of fulminant hepatitis, hepatic necrosis, encephalopathy, and death with propylthiouracil and thiamazole. Therapy should be withdrawn if hepatic disorders occur.

Other adverse effects sometimes seen with the thiourea antithyroid compounds include hair loss, a lupus-like syndrome, myopathy, vasculitis, nephritis, and taste disturbances. Drowsiness, paraesthesia, neuritis, oedema, skin pigmentation changes, sialadenopathy, and lymphadenopathy can also occur. Creatine phosphokinase values should be measured if patients develop myalgia.

Excessive doses of antithyroid drugs may cause hypothyroidism and goitre; the dose should be reduced, or therapy interrupted. High doses in pregnancy may result in fetal hypothyroidism and goitre (see Pregnancy, p. 2336.1).

Breast feeding. The safety of breast feeding during maternal treatment depends partly on how much drug is distributed into the breast milk. Thiourea antithyroid drugs may be used with care in breast-feeding mothers; neonatal development and thyroid function of the infant should be closely monitored and the lowest effective dose used.

Propylthiouracil has been preferred to carbimazole or thiamazole since it enters breast milk less readily.[1-3] In a small study[4] of breast-feeding mothers taking doses of propylthiouracil as high as 750 mg daily for Graves' disease, no adverse effects were seen on the thyroid status of their infants.

Thiamazole enters breast milk freely, with plasma to milk ratios of almost one.[3,5] The infant's intake of thiamazole after maternal use of carbimazole (or thiamazole) might be greatly reduced by discarding the breast milk produced 2 to 4 hours after a dose,[6] since the highest concentration was found at this time. Two studies found no adverse effects on thyroid function,[7,8] thyroid hormone levels,[7] or physical and intellectual development, in breast-fed infants during up to 6 months[7] to 1 year[8] of maternal treatment with thiamazole. Maximum maternal daily doses of 10 mg of thiamazole,[3] 15 mg of carbimazole, and 150 mg of propylthiouracil[9] have been recommended, although thiamazole 20 to 30 mg has been given to thyrotoxic lactating women for the first month of a year of therapy with no observable adverse effects on the thyroid function of their breast-fed infants.[10] Despite stating that goitre has been associated with the use of carbimazole, the last available guidance from the American Academy of Pediatrics considered the use of all three drugs to be compatible with breast feeding.[11]

1. Kampmann JP, *et al.* Propylthiouracil in human milk: revision of a dogma. *Lancet* 1980; **i:** 736–8.
2. Johansen K, *et al.* Excretion of methimazole in human milk. *Eur J Clin Pharmacol* 1982; **23:** 339–41.
3. Cooper DS. Antithyroid drugs: to breast-feed or not to breast-feed. *Am J Obstet Gynecol* 1987; **157:** 234–5.
4. Momotani N, *et al.* Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. *Clin Endocrinol (Oxf)* 2000; **53:** 177–81.
5. Cooper DS, *et al.* Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984; **58:** 473–9.
6. Rylance GW, *et al.* Carbimazole and breastfeeding. *Lancet* 1987; **i:** 928.
7. Azizi F. Effect of methimazole treatment of maternal thyrotoxicosis on thyroid function in breast-feeding infants. *J Pediatr* 1996; **128:** 855–8.
8. Azizi F, *et al.* Thyroid function and intellectual development of infants nursed by mothers taking methimazole. *J Clin Endocrinol Metab* 2000; **85:** 3233–8.
9. Lamberg B-A, *et al.* Antithyroid treatment of maternal hyperthyroidism during lactation. *Clin Endocrinol (Oxf)* 1984; **21:** 81–7.
10. Azizi F, Redayati M. Thyroid function in breast-fed infants whose mothers take high doses of methimazole. *J Endocrinol Invest* 2002; **25:** 493–6.
11. 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 18/05/05)

Effects on the blood. While **leucopenia** is considered to be a common adverse effect of the thiourea antithyroid drugs, occurring in up to a quarter of patients, it is usually mild and improves as treatment continues.[1]

Agranulocytosis, a more serious hazard, is usually reported to affect 0.03% of patients in Europe,[2] who are mostly treated with carbimazole. However, the incidence has been reported to be higher (0.4%) in areas where thiamazole is used.[3,4] Fatalities have been reported.[1,2,4,5] Although a direct toxic effect had been suggested, the agranulocytosis associated with the thiourea drugs is generally considered to be immunologically mediated.[1,6] The onset of agranulocytosis is usually rapid and monitoring of the blood count is not always of predictive value;[3] routine monitoring is not indicated.[2] Agranulocytosis has occurred in patients receiving propylthiouracil for a second time who had no such complications in their first course of therapy.[7] There is limited evidence that agranulocytosis is more common at higher doses, and in older patients. However, this has not been proven conclusively.[1] In fact, life-threatening agranulocytosis and hepatotoxicity during initiation of a standard dose of carbimazole has been described.[8]

There have been some case reports of **aplastic anaemia** being produced by antithyroid drugs, but the excess risk associated with their use is considered to be very low[6,9] and complete recovery has been reported after withdrawal of the antithyroid drug. An immune mechanism has been implicated.

Carbimazole has produced **haemolytic anaemia.**[10] In this case the immune reaction was specific to carbimazole and could not be shown with thiamazole.

On very rare occasions patients taking propylthiouracil have had a reduction in prothrombin values and bleeding.[11-13] In one patient bleeding was linked to propylthiouracil-induced **thrombocytopenia.**[14]

1. Bartalena L *et al.* Adverse effects of thyroid hormone preparations and antithyroid drugs. *Drug Safety* 1996; **15:** 53–63.
2. CSM/MCA. Reminder: agranulocytosis with antithyroid drugs. *Current Problems* 1999; **25:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
3. Tajiri J, *et al.* Antithyroid drug-induced agranulocytosis: the usefulness of routine white blood cell count monitoring. *Arch Intern Med* 1990; **150:** 621–4.
4. Anonymous. Elaboration: drug-induced agranulocytosis–monitoring antithyroid treatment. *Drug Ther Bull* 1997; **35:** 88.
5. Anonymous. Drug-induced agranulocytosis. *Drug Ther Bull* 1997; **35:** 49–52.
6. International Agranulocytosis and Aplastic Anaemia Study. Risk of agranulocytosis and aplastic anaemia in relation to use of antithyroid drugs. *BMJ* 1988; **297:** 262–5.
7. Shiran A, *et al.* Propylthiouracil-induced agranulocytosis in four patients previously treated with the drug. *JAMA* 1991; **266:** 3129–30.
8. Vilchez FJ, *et al.* Concomitant agranulocytosis and hepatotoxicity after treatment with carbimazole. *Ann Pharmacother* 2006; **40:** 2059–63.
9. Bishara J. Methimazole-induced aplastic anemia. *Ann Pharmacother* 1996; **30:** 684.
10. Salama A, *et al.* Carbimazole-induced immune haemolytic anaemia: role of drug-red blood cell complexes for immunization. *Br J Haematol* 1988; **68:** 479–82.
11. D'Angelo G, Le Gresley LP. Severe hypoprothrombinaemia after propylthiouracil therapy. *Can Med Assoc J* 1959; **81:** 479–81.
12. Naeye RL, Terrien CM. Hemorrhagic state after therapy with propylthiouracil. *Am J Clin Pathol* 1960; **34:** 254–7.
13. Gotta AW, *et al.* Prolonged intraoperative bleeding caused by propylthiouracil-induced hypoprothrombinemia. *Anesthesiology* 1972; **37:** 562–3.
14. Ikeda S, Schweiss JF. Excessive blood loss during operation in the patient treated with propylthiouracil. *Can Anaesth Soc J* 1982; **29:** 477–80.

Effects on the cardiovascular system. A study found that the use of antithyroid drugs was associated with a three-fold increased risk of sudden cardiac death. The authors stated that, while this effect might be caused directly by the drugs, this was unlikely since different drugs were involved and a plausible biological mechanism was lacking. Underlying poorly controlled hyperthyroidism was suggested as a more likely cause, since some treated patients were found to have had low thyroid-stimulating hormone concentrations shortly before death.[1]

1. van Noord C, *et al.* Population-based studies of antithyroid drugs and sudden cardiac death. *Br J Clin Pharmacol* 2009; **68:** 447–54.

Effects on the ears. Earache, high-frequency hearing loss, and tinnitus in a patient with Graves' disease were attributed to hypersensitivity to carbimazole;[1] hearing loss, but not the tinnitus, resolved when carbimazole was replaced with propylthiouracil. However, in another case,[2] propylthiouracil was associated with bilateral sensorineural hearing loss, which was thought to be caused by cochlear dysfunction from small-vessel vasculitis that locally compromised inner ear blood flow. Antineutrophil cytoplasmic antibodies (ANCA) were seen in the serum. ANCA concentrations returned to within normal limits and hearing loss was greatly improved after propylthiouracil was stopped and high-dose methylprednisolone was given.

1. Hill D, *et al.* Hearing loss and tinnitus with carbimazole. *BMJ* 1994; **309:** 929.
2. Sano M, *et al.* Progressive bilateral sensorineural hearing loss induced by an antithyroid drug. *ORL J Otorhinolaryngol Relat Spec* 2004; **66:** 281–5.

Effects on the kidneys. Glomerulonephritis associated with the development of antineutrophil cytoplasmic antibodies has been reported in patients receiving thiourea antithyroid drugs.[1-6]

1. Vogt BA, *et al.* Antineutrophil cytoplasmic autoantibody-positive crescentic glomerulonephritis as a complication of treatment with propylthiouracil in children. *J Pediatr* 1994; **124:** 986–8.
2. D'Cruz D, *et al.* Antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis associated with anti-thyroid drug treatment. *Br J Rheumatol* 1995; **34:** 1090–1.
3. Yuasa S, *et al.* Antineutrophil cytoplasmic antibodies (ANCA)-associated crescentic glomerulonephritis and propylthiouracil therapy. *Nephron* 1996; **73:** 701–3.
4. Kudoh Y, *et al.* Propylthiouracil-induced rapidly progressive glomerulonephritis associated with antineutrophil cytoplasmic autoantibodies. *Clin Nephrol* 1997; **48:** 41–3.
5. Prasad GVR, *et al.* Propylthiouracil-induced diffuse proliferative lupus nephritis: review of immunological complications. *J Am Soc Nephrol* 1997; **8:** 1205–10.
6. Trimeche Ajmi S, *et al.* Benzylthiouracil-induced glomerulonephritis. *Case Report Med* 2009; **2009:** 687285.

Effects on the liver. Jaundice, usually cholestatic, has been reported with thiamazole and carbimazole.[1-5] An immune-mediated mechanism rather than a toxic reaction has been proposed. Hepatotoxicity with agranulocytosis has been reported with carbimazole (see Effects on the Blood above). Hepatitis (sometimes progressing to cirrhosis[6]) and hepatic necrosis have been associated with propylthiouracil,[6-9] sometimes with fatal consequences.[7,8] The FDA has evaluated postmarketing adverse events from 1969 to 2009 and identified 34 cases of severe liver injury associated with propylthiouracil.[10] These included 23 adult cases where 13 resulted in death and 5 patients needed a liver transplant. There were also 11 paediatric reports, including 2 deaths and 7 children needing a transplant. In one study[11] almost 30% of patients being treated with propylthiouracil developed asymptomatic liver changes (increased alanine aminotransferase values). Dose reduction resulted in a return to normal values in 13 of the 15 patients affected.

Despite reports of liver damage, propylthiouracil has been investigated in the treatment of patients with alcoholic liver disease (see p. 2344.1).

1. Becker CE, *et al.* Hepatitis from methimazole during adrenal steroid therapy for malignant exophthalmos. *JAMA* 1968; **206:** 1787–9.
2. Fischer MG, *et al.* Methimazole-induced jaundice. *JAMA* 1973; **223:** 1028–9.
3. Blom H, *et al.* A case of carbimazole-induced intrahepatic cholestasis. *Arch Intern Med* 1985; **145:** 1513–15.
4. Schmidt G, *et al.* Methimazole-associated cholestatic liver injury: case report and brief literature review. *Hepatogastroenterology* 1986; **33:** 244–6.
5. Arab DM, *et al.* Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab* 1995; **80:** 1083–5.
6. Özenirler S, *et al.* Propylthiouracil-induced hepatic damage. *Ann Pharmacother* 1996; **30:** 960–3.
7. Hanson JS. Propylthiouracil and hepatitis. Two cases and a review of the literature. *Arch Intern Med* 1984; **144:** 994–6.
8. Limaye A, Ruffolo PR. Propylthiouracil-induced fatal hepatic necrosis. *Am J Gastroenterol* 1987; **82:** 152–4.
9. Ichiki Y, *et al.* Propylthiouracil-induced severe hepatitis: a case report and review of the literature. *J Gastroenterol* 1998; **33:** 747–50.
10. FDA. Drug Safety Communication: new boxed warning on severe liver injury with propylthiouracil (issued 21st April, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm (accessed 29/06/10)

11. Liaw Y-F, *et al.* Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. *Ann Intern Med* 1993; 118: 424–8.

Effects on the lungs. Diffuse interstitial pneumonitis occurred in 2 patients given propylthiouracil[1] and a hypersensitivity reaction was suggested. Propylthiouracil and benzylthiouracil have also been implicated in cases of pulmonary haemorrhage associated with antineutrophil cytoplasmic antibody (ANCA) vasculitis.[2-5]

1. Miyazono K, *et al.* Propylthiouracil-induced diffuse interstitial pneumonitis. *Arch Intern Med* 1984; 144: 1764–5.
2. Ohtsuka M, *et al.* Propylthiouracil-induced alveolar haemorrhage associated with antineutrophil cytoplasmic antibody. *Eur Respir J* 1997; 10: 1405–7.
3. Dhillon SS, *et al.* Diffuse alveolar hemorrhage and pulmonary capillaritis due to propylthiouracil. *Chest* 1999; 116: 1485–8.
4. Thabet F, *et al.* ANCA-associated diffuse alveolar hemorrhage due to benzylthiouracil. *Eur J Pediatr* 2006; 165: 435–6.
5. Tu Y-L, *et al.* Occult pulmonary hemorrhage as a rare presentation of propylthiouracil-induced vasculitis. *Pediatrics* 2011; 127: e245–e249.

Effects on the muscles. Myositis with pain, weakness, and increased creatine kinase concentrations has been reported with carbimazole.[1,2] This effect might be explained by 'tissue hypothyroidism', and might respond to dosage reduction.[3]

1. Page SR, Nussey SS. Myositis in association with carbimazole therapy. *Lancet* 1989; i: 964.
2. Pasquier E, *et al.* Biopsy-proven myositis with microvasculitis in association with carbimazole. *Lancet* 1991; 338: 1082–3.
3. O'Malley B. Carbimazole-induced cramps. *Lancet* 1989; i: 1456.

Hypersensitivity. Many of the adverse effects associated with the thiourea antithyroid drugs appear to have an immune basis. These effects may be associated with polyarthritis[1] or hypersensitivity vasculitis.[2-7] The latter is sometimes severe and multisystemic, and fatalities have occurred.

Hypersensitivity reactions may also be associated with the development of antineutrophil cytoplasmic antibodies (ANCA), or sometimes with a lupus-like syndrome with or without the presence of antinuclear antibodies.[2,5]

Serum sickness with arthralgias and raised immunoglobulin M (IgM) concentrations has been reported with thiamazole,[8] and the production of antibodies to insulin, resulting in episodes of hypoglycaemia, has been associated with thiamazole[9] and carbimazole.[10]

The thiourea antithyroid drugs all contain a thioamide group and cross-sensitivity between them might be expected. In particular, complete cross-reactivity may be expected between thiamazole and carbimazole since the latter is converted *in vivo* to thiamazole, although one report[11] suggests this is not necessarily the case. Cross-sensitivity between propylthiouracil and carbimazole[12] or thiamazole[13] has been reported but the incidence and clinical importance is not clear. Although it has been suggested that carbimazole or thiamazole may be substituted for propylthiouracil in hypersensitive patients, it is safer to stop antithyroid drugs in such patients.[12]

1. Bajaj S, *et al.* Antithyroid arthritis syndrome. *J Rheumatol* 1998; 25: 1235–9.
2. Kawachi Y, *et al.* ANCA-associated vasculitis and lupus-like syndrome caused by methimazole. *Clin Exp Dermatol* 1995; 20: 345–7.
3. Chastain MA, *et al.* Propylthiouracil hypersensitivity: report of two patients with vasculitis and review of the literature. *J Am Acad Dermatol* 1999; 41: 757–64.
4. Gunton JE, *et al.* Clinical case seminar: antithyroid drugs and antineutrophil cytoplasmic antibody positive vasculitis. A case report and review of the literature. *J Clin Endocrinol Metab* 1999; 84: 13–16.
5. Mathieu E, *et al.* Systemic adverse effect of antithyroid drugs. *Clin Rheumatol* 1999; 18: 66–8.
6. Dolman KM, *et al.* Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. *Lancet* 1993; 342: 651–2.
7. ten Holder SM, *et al.* Cutaneous and systemic manifestations of drug-induced vasculitis. *Ann Pharmacother* 2002; 36: 130–47.
8. Van Kuyk M, *et al.* Methimazole-induced serum sickness. *Acta Clin Belg* 1983; 38: 68–9.
9. Hakamata M, *et al.* Insulin autoimmune syndrome after the third therapy with methimazole. *Intern Med* 1995; 34: 410–12.
10. Burden AC, Rosenthal FD. Methimazole and insulin autoimmune syndrome. *Lancet* 1983; ii: 1311.
11. Kroll H, *et al.* Drug-dependent antibodies against the prodrug carbimazole do not react with the metabolite thiamazole. *Blood* 2001; 97: 2186–7.
12. Smith A, *et al.* Cross sensitivity to antithyroid drugs. *BMJ* 1989; 298: 1253.
13. De Weweire A, *et al.* Failure to control hyperthyroidism with a thionamide after potassium perchlorate withdrawal in a patient with amiodarone associated thyrotoxicosis. *J Endocrinol Invest* 1987; 10: 529.

Pregnancy. Thiourea antithyroid drugs have been used successfully in pregnancy, although there are risks associated with their use (see Hyperthyroidism, p. 2332.2).

Thiamazole (the metabolite of carbimazole) has been the drug most frequently involved in the few reports of congenital defects following maternal use of such compounds. Several infants exposed to thiamazole *in utero* have been born with scalp defects (aplasia cutis congenita—a localised absence of skin at birth)[1,2] although hyperthyroidism itself may give rise to such defects.[3] Individual cases of other congenital defects associated with thiamazole have included choanal atresia (an upper respiratory-tract defect), oesophageal atresia, and tracheo-oesophageal fistula[3] but the incidence of congenital abnormalities is not increased compared with the general population.[4]

Aplasia cutis congenita and choanal atresia (the latter with coarctation of the aorta) have also been reported after maternal exposure to carbimazole in the first trimester.[5] Other reported major malformations have included abdominal wall defects such as gastroschisis (or laparoschisis)[5,6] and omphalocele; digestive malformation has occurred, manifesting as a patent omphalomesenteric duct.[5] Other reported malformations include facial dysmorphisms, a high-arched palate, and an anomalous ear helix.[5]

A controlled cohort study concluded that propylthiouracil did not appear to be a major human teratogen.[7] However, the risk is unclear, due to a lack of data,[8] and US licensed product information states that cases of maternal and neonatal liver failure sometimes fatal, have been associated with the use of propylthiouracil. As with carbimazole and thiamazole, aplasia cutis congenita has also been reported after maternal use of propylthiouracil.[9] A case-control analysis[8] found maternal propylthiouracil exposure in the first trimester to be associated with situs inversus with or without dextrocardia, unilateral kidney agenesis or dysgenesis, and cardiac outflow defects. However, further studies were considered necessary to evaluate these associations because of the low number of affected subjects. The use of carbimazole or thiamazole was found to be significantly associated with omphalocele and choanal atresia, which was consistent with previous reports.

There have been some reports of neonates exposed to thiourea antithyroid drugs *in utero* displaying signs of hypothyroidism including goitre.[7,10,11]

1. Milham S. Scalp defects in infants of mothers treated for hyperthyroidism with methimazole or carbimazole during pregnancy. *Teratology* 1985; 32: 321.
2. Vogt T, *et al.* Aplasia cutis congenita after exposure to methimazole: a causal relationship? *Br J Dermatol* 1995; 133: 994–6.
3. Johnsson E, *et al.* Severe malformations in infant born to hyperthyroid woman on methimazole. *Lancet* 1997; 350: 1520.
4. Wing DA, *et al.* A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynecol* 1994; 170: 90–5.
5. Koenig D, *et al.* Birth defects observed with maternal carbimazole treatment: six cases reported to Nice's Pharmacovigilance Center. *Ann Endocrinol (Paris)* 2010; 71: 535–42.
6. Guignon A-M, *et al.* Carbimazole-related gastroschisis. *Ann Pharmacother* 2003; 37: 829–31.
7. Rosenfeld H, *et al.* Pregnancy outcome, thyroid dysfunction and fetal goitre after in utero exposure to propylthiouracil: a controlled cohort study. *Br J Clin Pharmacol* 2009; 68: 609–17.
8. Clementi M, *et al.* SAFE-Med Study Group. Treatment of hyperthyroidism in pregnancy and birth defects. *J Clin Endocrinol Metab* 2010; 95: E337–E341.
9. Löllgen RM, *et al.* Aplasia cutis congenita in surviving co-twin after propylthiouracil exposure in utero. *J Pediatr Endocrinol Metab* 2011; 24: 215–18.
10. O'Doherty MJ, *et al.* Treating thyrotoxicosis in pregnant or potentially pregnant women. *BMJ* 1999; 318: 5–6.
11. Masiukiewicz US, Barrow GN. Hyperthyroidism in pregnancy: diagnosis and treatment. *Thyroid* 1999; 9: 647–52.

Pharmacokinetics

The pharmacokinetics of carbimazole and thiamazole can be considered together since carbimazole is rapidly and completely metabolised to thiamazole in the body. The antithyroid activity of carbimazole is dependent upon this conversion to thiamazole.

Carbimazole and thiamazole are rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 1 to 2 hours after oral doses.

Thiamazole is concentrated in the thyroid gland; since duration of action is more closely related to the intrathyroidal drug concentration than plasma half-life, prolonged antithyroid activity results from single daily doses. Thiamazole is moderately bound to plasma proteins.

Thiamazole has an elimination half-life from plasma of about 3 to 6 hours and is metabolised, probably by the liver, and excreted in the urine. Less than 12% of a dose of thiamazole may be excreted as unchanged drug. 3-Methyl-2-thiohydantoin has been identified as a metabolite of thiamazole. The elimination half-life may be increased in hepatic and renal impairment.

Thiamazole crosses the placenta and is distributed into breast milk.

References to the pharmacokinetics of carbimazole and thiamazole.

1. Skellern GG, *et al.* The pharmacokinetics of methimazole after oral administration of carbimazole and methimazole, in hyperthyroid patients. *Br J Clin Pharmacol* 1980; 9: 137–43.
2. Kampmann JP, Hansen JM. Clinical pharmacokinetics of antithyroid drugs. *Clin Pharmacokinet* 1981; 6: 401–28.
3. Jansson R, *et al.* Intrathyroidal concentrations of methimazole in patients with Graves' disease. *J Clin Endocrinol Metab* 1983; 57: 129–32.
4. Cooper DS, *et al.* Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984; 58: 473–9.
5. Jansson R, *et al.* Pharmacokinetic properties and bioavailability of methimazole. *Clin Pharmacokinet* 1985; 10: 443–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Neo-Mercazole; *Austria*: Carbistad†; *Denm.*: Neo-Mercazole; *Fin.*: Tyrazol; *Fr.*: Neo-Mercazole; *Gr.*: Thyrostat; *Hong Kong*: Cazole; Neo-Mercazole; *India*: Anti-Thyrox; Neo-Mercazole; *Indon.*: Neo-Mercazole; *Irl.*: Neo-Mercazole; *Malaysia*: Thymazole; *Norw.*: Neo-Mercazole; *NZ*: Neo-Mercazole; *Philipp.*: Anti-Thyrox; Carbinom; Neomercazole; Neomerdin; *S.Afr.*: Neo-Mercazole; *Singapore*: Camazol; *Spain*: Neo Tomizol; *Switz.*: Neo-Mercazole; *UK*: Neo-Mercazole†; *Ukr.*: Espa-Carb (Эспа-карб).

Pharmacopoeial Preparations
BP 2014: Carbimazole Tablets.

Dibromotyrosine

Dibromotirosina; Дибромотирозин.
3,5-Dibromo-L-tyrosine.
$C_9H_9Br_2NO_3$=339.0
CAS — 300-38-9.
ATC — H03BX02.
ATC Vet — QH03BX02.
UNII — QD49LEP46E.

Profile

Dibromotyrosine is an antithyroid drug used in the treatment of hyperthyroidism (p. 2332.2) in oral doses of 300 to 900 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

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

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

Iodine

Iaidín; Iod; Iode; Ïodin; Iodio; Iodiu; Iodium; Iodo; Iodum; Jód; Jod; Joð; Jodas; Jodi; Jodium; Jods; Jodum; Jood; Iyot; Yodo; Йод.
I_2=253.80894
CAS — 7553-56-2.
ATC — D08AG03.
ATC Vet — QD08AG03.
UNII — 9679TC07X4 (iodine); 09G4I6V86Q (iodine ion).

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

Ph. Eur. 8: (Iodine). Greyish-violet, brittle plates or fine crystals, with a metallic sheen. It is slowly volatile at room temperature. Very slightly soluble in water; soluble in alcohol; slightly soluble in glycerol; very soluble in concentrated solutions of iodides.

USP 36: (Iodine). Heavy, greyish-black plates or granules with a metallic sheen and a characteristic odour. Soluble 1 in 3000 of water, 1 in 13 of alcohol, 1 in 4 of carbon disulfide, and 1 in 80 of glycerol; freely soluble in chloroform, in ether, and in carbon tetrachloride; soluble in solutions of iodides. Store in airtight containers.

Incompatibility. With acetone, iodine forms a pungent irritating compound.

Potassium Iodate

Iodate de Potassium; Iodato de Potássio; Iodato di Potassio; Iodato potásico; Kaliumiodat; Kaliumjodaat; Kaliumjodaatti; Potasu jodan; Yodato potásico; Йодат Калия.
KIO_3=214.0
CAS — 7758-05-6.
UNII — 1139E44NHL.

Pharmacopoeias. In *Br.*, *Chin.*, and *It.*

BP 2014: (Potassium Iodate). A white crystalline powder with a slight odour. Slowly soluble in water; insoluble in alcohol. A 5% solution in water has a pH of 5.0 to 8.0.

Potassium Iodide

Iodeto de Potássio; Iodur de Potassi; Ioduro di Potassio; Ioduro potásico; Jodid draselný; Kalii Iodetum; Kalii Iodidum; Kalii Jodidum; Kālija jodīds; Kalijum Jodid; Kalio jodidas; Kalium Iodatum; Kalium Jodatum; Kaliumiodid; Kaliumjodid; Kálium-jodid; Kaliumjodide; Kaliumjodidi; Pot. Iod.; Potassii Iodidum; Potassium, Iodure de; Potasu jodek; Potasyum İyodür; Yoduro de Potasio; Yoduro potásico; Калиев йодид; Йодид Калия.
KI=166.0
CAS — 7681-11-0.
ATC — R05CA02; S01XA04; V03AB21.

ATC Vet — QR05CA02; QS01XA04; QV03AB21.
UNII — 1C4QK22F9J.

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

Ph. Eur. 8: (Potassium Iodide). A white or almost white powder or colourless crystals. Very soluble in water; soluble in alcohol; freely soluble in glycerol. Protect from light.

USP 36: (Potassium Iodide). Hexahedral crystals, either transparent and colourless or somewhat opaque and white, or a white, granular powder. It is slightly hygroscopic. Soluble 1 in 0.7 of water and 1 in 0.5 of boiling water, 1 in 22 of alcohol, and 1 in 2 of glycerol. Its solutions are neutral or alkaline to litmus.

Sodium Iodide

Iodeto de Sódio; Iodur de Sodi; Ioduro di Sodio; Ioduro sódico; Jodid sodný; Natrii iodetum; Natrii iodidum; Natrii jodidum; Natrijum Jodid; Natrio jodidas; Natrium iodatum; Natriumiodid; Natriumjodid; Natrium-jodid; Natriumjodide; Natriumjodidi; Sod. iod.; Sodii iodidum; Sodium (Iodure de); Sodium, Iodure de; Sodu jodek; Sodyum Iyodür; Yoduro de Sodio; Yoduro sódico; Йодид Натрия.

NaI=149.9.
CAS — 7681-82-5.
UNII — F5WR8N145C.

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

Ph. Eur. 8: (Sodium Iodide). Colourless crystals or white or almost white, crystalline powder. It is hygroscopic. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Sodium Iodide). Colourless, odourless crystals, or white crystalline powder. It is deliquescent in moist air and develops a brown tint upon decomposition. Soluble 1 in 0.6 of water, 1 in 2 of alcohol, and 1 in 1 of glycerol. Store in airtight containers.

Uses and Administration

Iodine is an essential trace element in the human diet, necessary for the formation of thyroid hormones (see p. 2332.1), and consequently it is used in iodine deficiency and thyroid disorders. It also has antimicrobial activity.

For the prophylaxis and treatment of **iodine deficiency disorders** (below) it may be given as potassium iodide, potassium iodate, or as iodised oil. Sodium iodide has also been used. Each g of potassium iodide represents about 6 mmol of potassium and of iodine. Each g of sodium iodide represents about 6.7 mmol of sodium and of iodine. Each g of potassium iodate represents about 4.7 mmol of potassium and of iodine.

In the pre-operative management of **hyperthyroidism** (p. 2332.2) iodine and iodides are used with antithyroid drugs such as carbimazole, thiamazole, or propylthiouracil. Such use has been thought to render the thyroid firm and avoid the increased vascularity and friability (with increased risk of haemorrhage) that may result from the use of an antithyroid drug alone. However, there is little evidence of a beneficial effect.

Iodine may be given as a solution with potassium iodide (Aqueous Iodine Oral Solution BP 2014; Lugol's Solution or Strong Iodine Solution USP 36) which contains in each mL 130 mg of free and combined iodine; a dose of 0.1 to 0.3 mL in milk or water is given three times daily for 10 to 14 days. Alternatively, potassium iodide has been given in doses of up to 250 mg three times daily with food. Solutions of potassium iodide intended for oral use should be given well diluted to avoid gastric irritation. Potassium iodide may also be given 1 hour after an antithyroid drug as part of the management of thyroid storm; doses as high as 500 mg every 4 hours have been suggested.

Radioactive sodium iodide (see Iodine-131, p. 2225.3) is also used for the treatment of hyperthyroidism, especially when medical treatment or compliance is problematic, in patients with cardiac disease, or in patients who relapse after thyroidectomy.

Potassium iodide or potassium iodate are taken orally for **radiation protection** (p. 2338.1) to saturate the thyroid when uptake of radio-iodine by the gland is not desired.

Iodine has a powerful bactericidal action. It is also active against fungi, viruses, protozoa, cysts, and spores. Potassium iodide has been used in the treatment of fungal infections such as sporotrichosis (below). Iodine is used as an **antiseptic** and **disinfectant** generally as a 2% or 2.5% solution. Its activity is reduced in the presence of organic matter, though not to the same extent as with the other halogen disinfectants. If industrial methylated spirit is used for the solution, it should be free from acetone, with which iodine forms an irritant and lachrymatory compound. Iodine solutions may be applied to small wounds or abrasions as well as to unbroken skin, but an iodophore such as povidone-iodine (p. 1767.1) may be preferred.

Iodine may also be used to sterilise drinking water; see below. Tablets containing tetraglycine hydroperiodide (p. 1771.3) may be preferred.

When iodine combines chemically it is decolorised and so-called colourless iodine preparations do not have the disinfectant properties of iodine.

Iodine stains the skin a deep reddish-brown; the stain can be readily removed by dilute solutions of alkalis or sodium thiosulfate. A dilute solution of iodine (Schiller's Iodine) may also be used as a **diagnostic** stain in colposcopy.

There have been many other uses of iodine and iodides. Iodides have long been used as ingredients of expectorant mixtures (see Cough, p. 1651.2) but there has been concern over their safety because of their potential for thyroid suppression. A diatomic iodine formulation has been investigated for the treatment of fibrocystic breast disease. Iodinated organic compounds including iodised oil are used as X-ray contrast media (see Radiographic Contrast Media, p. 1580.1). Potassium iodide has been given in the treatment of Sweet's syndrome (acute febrile neutrophilic dermatosis). A mixture of iodine and sodium iodide is used as sclerotherapy for varicose veins (p. 2564.1).

Administration in children. For dosage of iodine or iodide in children, see Iodine Deficiency Disorders (below) and Radiation Protection (p. 2338.1), respectively.

Disinfection of water. Iodine may be used to sterilise drinking water although WHO recommends its use only short-term or as an emergency measure (see p. 1731.3). It may be useful for individual water treatment where surface water is ingested or water quality is questionable. Iodine for this purpose is available in many forms including alcoholic solutions (tinctures), tablets, and iodine resins. Iodine resins may be incorporated into filters.[1] Five drops of a 2% alcoholic solution added to about one litre (one US quart) of water is reported to kill most pathogens; the water must stand for a minimum of 30 minutes before use; however, longer contact is required to kill *Giardia* cysts, especially if the water is cold, and it is ineffective against *Cryptosporidium*.[2] Some have commented that since the volume of a drop may differ between delivery devices, this may not yield a concentration of about 8 mg/litre, which is required for inactivation of *Giardia* cysts.[3]

Iodine-based water treatments are not recommended for patients who have or are at increased risk of iodine-induced thyroid disorders. Where iodine water disinfection is used, its use should be limited in euthyroid patients to 3 months if high concentrations of iodine (5 to 32 mg/litre) are produced. However, coupled with periodic monitoring of thyroid function, lower concentrations of iodine in water (1 to 2 mg/litre) can be safely used for long periods of time.[1]

1. Backer H, Hollowell J. Use of iodine for water disinfection: iodine toxicity and maximum recommended dose. *Environ Health Perspect* 2000; 108: 679–84.
2. WHO. Preventing traveller's diarrhoea: how to make drinking water safe (issued 2005). Available at: http://www.who.int/water_sanitation_health/hygiene/envsan/sdwtravel.pdf (accessed 24/06/11)
3. Goodyer L. Food and water hygiene for the traveller. *Pharm J* 2000; 264: 134–9.

Fungal infections. Potassium iodide is used in the treatment of cutaneous sporotrichosis (p. 568.3), although how it acts is unclear since antifungal activity was not found *in vitro* against *Sporothrix schenkii*. It has also been shown to be effective in the treatment of phycomycosis caused by *Basidiobolus haptosporus*[1,2] but again the mode of action is unclear.[3] Mycetomas due to *Pseudallescheria boydii* are usually treated with azole antifungals such as itraconazole (p. 567.1) but there is a report of response to oral potassium iodide.[4] The authors suggested that its action might be due to proteolysis or activation of myeloperoxidase. Potassium iodide is usually given orally in a gradually increasing dosage up to the limit of tolerance. The WHO[5] recommended initial dose is 1 mL [1 g] of a saturated solution of potassium iodide (1 g/mL) given three times daily; this may be increased by 1 mL daily, to a maximum daily dose of 10 mL. Treatment should be continued for at least 4 weeks after the disappearance or stabilisation of the lesions.

Potassium iodide and sodium iodide have been tried by local intracavitary instillation for the treatment of life-threatening haemoptysis from pulmonary aspergillomas.[6] Mechanical factors may have accounted for a beneficial effect rather than any antifungal action. Aspergillomas are usually managed conservatively or, in more severe disease, with antifungals or surgery (see p. 563.1).

1. Kelly S, *et al.* Subcutaneous phycomycosis in Sierra Leone. *Trans R Soc Trop Med Hyg* 1980; 74: 396–7.
2. Kamalam A, Thambiah AS. Muscle invasion by Basidiobolus haptosporus. *Sabouraudia* 1984; 22: 273–7.
3. Yangco BG, *et al.* In vitro susceptibilities of human and wild-type isolates of Basidiobolus and Conidiobolus species. *Antimicrob Agents Chemother* 1984; 25: 413–16.
4. Khan FA, *et al.* Multiple subcutaneous mycetomas caused by *Pseudallescheria boydii*: response to therapy with oral potassium iodide solution. *J Infect* 2010; 60: 178–81.
5. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 28/04/10)
6. Rumbak M, *et al.* Topical treatment of life threatening haemoptysis from aspergillomas. *Thorax* 1996; 51: 253–5.

Iodine deficiency disorders. Iodine is an essential trace element required for thyroid hormone production. In the UK the reference nutrient intake (RNI) for adults is 140 micrograms (1.1 micromoles) of iodine daily[1] and in the USA the recommended dietary allowance (RDA) is 150 micrograms daily.[2] A full explanation of the terms RNI and RDA can be found under Human Requirements of Vitamins, p. 2046.1.

The International Council for Control of Iodine Deficiency Disorders, UNICEF, and WHO recommend[3,4] the following daily iodine intakes:

- 90 micrograms for infants and children up to 59 months of age
- 120 micrograms for children in their 6th to 12th year
- 150 micrograms for adolescents and adults
- 200 to 250 micrograms for pregnant and lactating women

When iodine requirements are not met, a range of disorders can develop. These iodine deficiency disorders include endemic goitre (enlargement of the thyroid), endemic cretinism (a syndrome characterised by deaf-mutism, intellectual deficit, spasticity, and sometimes hypothyroidism), impaired mental function in children and adults, and an increased incidence of still-births as well as perinatal and infant mortality.[4-6]

Iodine deficiency disorders can be prevented by iodine supplementation. The incidence of endemic goitre, endemic cretinism, mental retardation, pregnancy loss, and infant mortality can be reduced and some of the effects of established iodine deficiency ameliorated, with only modest risks.[6,7]

Although various methods of iodine supplementation, including iodination of water and bread, as well as giving potassium iodide or iodate, have been investigated, the two methods generally used are iodination of culinary salt and the use of iodised oil.[4,6,8]

Salt may be iodinated by the addition of potassium iodide or potassium iodate.[6,9] The concentration used in different countries varies over a wide range from 10 to about 100 ppm of elemental iodine; 20 to 40 ppm has been suggested as being a more appropriate concentration.[6]

The chief alternative to supplementation with iodinated salt is *iodised oil*, usually by intramuscular injection; it is useful where salt consumption is unreliable or inadequate or where immediate action is necessary to correct severe iodine deficiency.[4,6,9] A commonly used type of iodised oil has been a poppyseed oil containing about 38% w/w or 480 mg/mL of iodine (see Iodised Oil, p. 1589.1). Some countries have produced iodised oil based on alternatives such as peanut or rapeseed oil.[10,11] Single intramuscular doses can provide adequate protection from iodine deficiency for up to 3 years. WHO has recommended[9] the following intramuscular doses of iodised oil (480 mg/mL iodine):

- 190 mg for infants up to 1 year
- 380 mg for children and adults up to age 45

Subjects over the age of 45 years and those with nodular goitre are susceptible to hyperthyroidism when given iodine, and iodised oil may not be a suitable means of supplementation. If it is used, doses of 76 mg are given.[9]

Iodised oil may also be given orally. The evidence suggests that oral iodised oil is as effective as intramuscular for preventing iodine deficiency disorders in children.[8] WHO recommends[9] the following oral doses:

- a single dose of 100 mg in infants up to 1 year
- 200 mg once yearly in children from 1 to 5 years
- 400 mg once yearly for children over 6 years
- 400 mg once yearly for adults, except during pregnancy, when
- a single dose of 200 mg is given to pregnant women

Iodine or iodides may suppress neonatal thyroid function and it is generally recommended that iodine compounds should be avoided during **pregnancy**. However, where it is essential to prevent neonatal goitre and cretinism, iodine supplementation should not be withheld from pregnant women.[12,13] Iodine supplementation has been found to be effective in preventing brain-damage in the fetus provided it is given to the mother in the first or second trimester;[12] treatment later in pregnancy was not effective in improving neurological status, although some developmental improvement was seen and hypothyroidism will be corrected. WHO has stated that in areas where iodine deficiency disorders are moderate to severe, iodised oil given either before or at any stage of gestation is beneficial.[9,13] The following doses are recommended[9] during pregnancy and for one year postpartum:

- 480 mg intramuscularly once yearly, *or*
- 300 to 480 mg orally once yearly, *or*
- 100 to 300 mg orally every 6 months

Non-pregnant fertile women may be given:

- 480 mg intramuscularly once yearly, *or*
- 400 to 960 mg orally once yearly, *or*
- 200 to 480 mg orally every 6 months

Indirect iodine supplementation, by addition of potassium iodate to the water used to irrigate crops, has been tried in areas of iodine deficiency where other methods had proved difficult to implement.[14] Iodine-fortified animal fodder has also increased the iodine content of foods derived from animal sources.[6]

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 Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 23/06/11)
3. WHO. Iodine. In *Vitamin and mineral requirements in human nutrition*. 2nd ed. Geneva: WHO, 2004: 303–17. Also available at: http://libdoc.who.int/publications/2004/9241546123_chap16.pdf (accessed 23/06/11)
4. ICCIDD/UNICEF/WHO. *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination: a guide for programme managers*. 3rd ed. Geneva: WHO, 2007. Also available at: http://whqlibdoc.who.int/publications/2007/9789241595827_eng.pdf (accessed 23/06/11)
5. WHO. Iodine status worldwide: WHO Global Database on Iodine Deficiency. Geneva: WHO, 2004. Also available at: http://whqlibdoc.who.int/publications/2004/9241592001.pdf (accessed 23/06/11)
6. Zimmermann MB. Iodine deficiency. *Endocr Rev* 2009; 30: 376–408.
7. Delange F, Lecomte P. Iodine supplementation: benefits outweigh risks. *Drug Safety* 2000; 22: 89–95.
8. Angermayr L, Clar C. Iodine supplementation for preventing iodine deficiency disorders in children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 23/06/11).
9. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 23/06/11)
10. Ingenbleek Y, *et al*. Iodised rapeseed oil for eradication of severe endemic goitre. *Lancet* 1997; 350: 1542–5.
11. Untoro J, *et al*. Efficacy of different types of iodised oil. *Lancet* 1998; 351: 752–3.
12. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996; 74: 101–8.
13. WHO. Safe use of iodized oil to prevent iodine deficiency in pregnant women. *Bull WHO* 1996; 74: 1–3.
14. Cao X-Y, *et al*. Iodination of irrigation water as a method of supplying iodine to a severely iodine-deficient population in Xinjiang, China. *Lancet* 1994; 344: 107–10.

Radiation protection. Giving a radiologically stable form of iodine to saturate the thyroid gland confers thyroid protection from iodine radionuclides.[1,2]

Potassium iodide or iodate may be used when thyroid protection from a *medical procedure* involving radio-iodine is needed. Oral doses of potassium iodide 130 mg or potassium iodate 170 mg (to provide about 100 mg of iodine) are given daily, starting 24 to 48 hours before the procedure. Treatment is continued until the estimated activity of radio-iodine in the body has fallen to acceptable levels, which may be up to 15 days after the procedure depending on the radiopharmaceutical formulation used.

In the event of a *nuclear accident* authorities in the USA recommend[1,3] an oral dose of 130 mg of potassium iodide daily in adults (including pregnant and lactating women). Daily doses should be given until risk of exposure has passed and adjunctive measures have been implemented. Recommended daily doses of potassium iodide for children are:

- up to 1 month of age, 16 mg
- 1 month to 3 years, 32 mg
- 3 to 12 years (up to 18 years if body-weight is less than 70 kg), 65 mg

In the UK the oral dose recommended[4] is a single dose of 100 mg of stable iodine (as 170 mg of potassium iodate) for adults (including pregnant women and women who are breast feeding) as soon as possible after exposure and before evacuation. Dosages for children are:

- 3 to 12 years, 50 mg of stable iodine (85 mg of potassium iodate)
- 1 month to 3 years, 25 mg of stable iodine (42.5 mg of potassium iodate)
- neonates, 12.5 mg of stable iodine (21.25 mg of potassium iodate)

In the event of prolonged exposure, repeated daily doses may become necessary. However, UK authorities advise that repeated doses should be avoided in neonates and pregnant and breast-feeding women because of the sensitivity of the thyroid in the neonate and fetus to large doses of iodine. They also advise that all neonates should be monitored for a few weeks after treatment with potassium iodate.

1. Halperin JA. Potassium iodide as a thyroid blocker— Three Mile Island today. *Drug Intell Clin Pharm* 1989; 23: 422–7.
2. Nauman J, Wolff J. Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. *Am J Med* 1993; 94: 524–32.
3. FDA Center for Drug Evaluation and Research. Guidance: potassium iodide as a thyroid blocking agent in radiation emergencies (issued December 2001). Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080542.pdf (accessed 23/06/11)
4. National Radiological Protection Board. Stable iodine prophylaxis: recommendations of the 2nd UK Working Group on Stable Iodine Prophylaxis. *Doc NRPB* 2001: 12 (3): 1–30. Also available at: http://www.hpa.org.uk/web/HPAwebfile/HPAweb_C/1194947336017 (accessed 23/06/11)

Adverse Effects and Treatment

Iodine and iodides have variable effects on the thyroid (see below) and can produce hyperthyroidism (the Iod-Basedow or Jod-Basedow phenomenon) as well as goitre and hypothyroidism; the latter have also occurred in infants born to mothers who had taken iodides during pregnancy.

Hypersensitivity reactions to iodides may include urticaria, angioedema, cutaneous haemorrhage or purpuras, fever, arthralgia, lymphadenopathy, and eosinophilia. Large doses or prolonged use of iodides may lead to a range of adverse effects, often called 'iodism', some of which resemble hypersensitivity reactions. Adverse effects include metallic taste, increased salivation, burning or painful mouth; there may be coryza-like symptoms, and swelling and inflammation of the throat and salivary glands. Eyes may be irritated and swollen and there may be increased lachrymation. Pulmonary oedema, dyspnoea, and bronchospasm may develop. Skin reactions include mild acneform eruptions or, more rarely, severe eruptions (iododerma). Other reported effects include depression, insomnia, impotence, headache, and gastrointestinal disturbances.

Retinal toxicity has been seen with overdose of potassium iodate.

Ingestion of iodine can also cause a metallic taste, thirst, and corrosive effects on the gastrointestinal tract; vomiting, abdominal pain, and bloody diarrhoea can occur. Systemic toxicity may lead to hypotension, tachycardia, fever, headache, delirium, metabolic acidosis, and renal impairment. Circulatory failure due to shock, pulmonary oedema, aspiration pneumonia, or asphyxiation can occur; fatalities have been reported. Oesophageal stricture is a possible complication if the patient survives the acute stage.

Victims of acute iodine poisoning have been given copious draughts of milk or starch mucilage; however, the UK National Poisons Information Service contra-indicates the use of gastric lavage, due to the corrosive nature of iodine. Sodium thiosulfate (usually as a 1% solution) will reduce iodine to the less toxic iodide. Activated charcoal may be considered in both iodine and iodide poisoning if the patient presents within 1 hour of ingestion.

Inhalation of iodine vapour is very irritating to mucous membranes, causing conjunctivitis and rhinitis; corrosive effects can lead to pulmonary oedema.

Effects on the thyroid. Iodide may be isolated by the body from a variety of sources, including an iodine-rich diet, or some disinfectants and drugs containing iodine (see also under Amiodarone, p. 1302.3). Although iodine is required for the production of thyroid hormones, excessive quantities can cause hyperthyroidism, or even paradoxical goitre and hypothyroidism.

The normal daily requirement ranges from 100 to 300 micrograms.[1,2] Quantities of 500 micrograms to 1 mg daily probably have no untoward effects on thyroid function in most cases.[2] When progressively larger doses are given there is an initial rise in thyroid hormone production, but at still higher doses, production decreases (the Wolff-Chaikoff effect). This effect is usually seen with doses of more than about 2 mg daily, but is normally transient, adaptation occurring on repeated dosage. In certain individuals a lack of adaptation produces a chronic inhibition of thyroid hormone synthesis leading to goitre and **hypothyroidism**.[1,2] Population studies looking at iodine intake have discovered an increased incidence of hypothyroidism, especially in those with previous iodine deficiency.[3,4]

Excess iodine may also induce **hyperthyroidism** (the Iod-Basedow or Jod-Basedow phenomenon). Iodine-induced hyperthyroidism has been associated with iodine prophylaxis programmes in developing countries.[5] The highest incidence of hyperthyroidism has been reported to occur 1 to 3 years after supplementation begins, with the incidence returning to normal within 3 to 10 years despite continued iodine exposure.[6] Elderly subjects and those with nodular goitres have been found to be at greatest risk.

To overcome any adverse effects on thyroid function as a result of iodine prophylaxis during **pregnancy**, WHO has issued guidelines on the safe use of iodised oil during gestation.[7,8] There is some evidence that the use of iodine-containing antiseptics on pregnant women and neonates may cause disturbances in thyroid function.[9,10]

1. Arthur JR, Beckett GJ. Thyroid function. *Br Med Bull* 1999; 55: 658–68.
2. WHO. Iodine. In *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 49–71.
3. Teng W, *et al*. Effect of iodine intake on thyroid diseases in China. *N Engl J Med* 2006; 354: 2783–93.
4. Pedersen IB, *et al*. An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study. *J Clin Endocrinol Metab* 2007; 92: 3122–7.
5. Delange F, *et al*. Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt. *Thyroid* 1999; 9: 545–56.
6. Fradkin JE, Wolff J. Iodide-induced thyrotoxicosis. *Medicine (Baltimore)* 1983; 62: 1–20.
7. WHO. Safe use of iodized oil to prevent iodine deficiency in pregnant women. *Bull WHO* 1996; 74: 1–3.
8. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996; 74: 101–8.
9. Linder N *et al*. Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997; 131: 434–9.
10. Weber G *et al*. Neonatal transient hypothyroidism: aetiological study. *Arch Dis Child Fetal Neonatal Ed* 1998; 79: F70–2.

Precautions

Caution is necessary if preparations containing iodine or iodides are taken for long periods, and such preparations should not be taken regularly during pregnancy except when iodine supplementation is required. Caution is also required when giving iodine or iodides to children. Patients over the age of 45 years or with nodular goitres are especially susceptible to hyperthyroidism when given iodine supplementation. Reduced doses should therefore be used and supplementation with iodised oil may not be appropriate.

Solutions of iodine applied to the skin should not be covered with occlusive dressings. The disinfectant activity of iodine is reduced by alkalis as well as by protein.

As iodine and iodides can affect the thyroid gland, their use may interfere with tests of thyroid function.

Breast feeding. Iodine is concentrated by the mammary gland into breast milk to ensure an adequate supply to the breast-fed infant. Since this is dependent on the maternal dietary intake,[1] WHO recommends a daily iodine intake of 200 micrograms for lactating women, see Iodine Deficiency Disorders, p. 2337.3.

The *BNFC* considers treatment with iodine or iodides to be a contra-indication to breast feeding. However, the last available guidance from the American Academy of Pediatrics[2] considered that such treatment was usually compatible with breast feeding although it was noted that goitre or effects on thyroid function had been reported. Any risk is not confined to oral treatment: transient neonatal hypothyroidism has been reported in a breast-fed infant whose mother was treated with iodine tampons,[3] and for a report of increased milk-iodine concentrations associated with vaginal povidone-iodine see p. 1767.2.

1. Semba RD, Delange F. Iodine in human milk: perspectives for infant health. *Nutr Rev* 2001; 59: 269–78.
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 18/05/05)
3. Casteels K, *et al*. Transient neonatal hypothyroidism during breastfeeding after post-natal maternal topical iodine treatment. *Eur J Pediatr* 2000; 159: 716–17.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium iodide as not porphyrinogenic when used as an antidote; it may be used as a drug of first choice and no precautions are needed.[1] No classification is offered when used in cough or cold preparations or in ophthalmological preparations.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/09/11)

Interactions

The effects of iodine and iodides on the thyroid may be altered by other compounds including amiodarone and lithium.

Pharmacokinetics

Iodine is slightly absorbed when applied to the skin. When taken orally, iodine preparations (which are converted to iodide) and iodides are transported to, and concentrated in, the thyroid gland (see p. 2332.1). Iodides not taken up by the thyroid are excreted mainly in the urine, with smaller amounts appearing in the faeces, saliva, and sweat. They cross the placenta and are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Jodid; *Braz.*: Fluidelan; Glitosslab†; Iodeton; Iodetoss; Iodex; Xarope Neo; *Canad.*: Micro I; Radblock; Sclerodine; *China*: Jindian (金典); *Cz.*: Kalijev†; *Fin.*: Jodix; *Ger.*: Jod beta; Jodetten†; Jodgamma; Jodid; Mono-Jod; Thyrotect†; *Gr.*: Jodosan; *Hung.*: Jod plus†; Jodid; Jodomax†; *India*: Collosol; *Indon.*: Yodsaben†; *Israel*: Iosat; *Ital.*: Chitodine†; Goccemed; *Mex.*: Yodolactina; *Neth.*: Kajodan; *Norw.*: Jodosan†; *Philipp.*: Ilens; Jodid; Vistalens; Vitreolent; *Pol.*: Jodid; Vitreolent; *Rus.*: Iodomarin (Йодомарин); Jodbalance (Йодбаланс); Jodid (Йодид); Microiodid (Микройодид); *Spain*: Yodafar; Yodiquer; Yoduk; *Thal.*: Pose-Iodophore†; *Turk.*: Tenturdiyot; *UK*: Biolodine; ThySat; *Ukr.*: Antistrumin (Антиструмин); Iodomarin (Йодомарин); Lugs (Люге); *USA*: Curity; Geri-Dyne; Iodoflex; Iodopen; Iosat; Pima; SSKI; Thyro-Block; ThyroSafe; ThyroShield.

Multi-ingredient Preparations. *Arg.*: Antikatarata Plus; *Austral.*: Asa Tones†; Gartech†; Haemo-Red; I-Folic; PM IQShield; *Austria*: Jodthyrox; *Braz.*: Bronquidex; Brontoss; Dermicon; Endo-

tussin†; Expec; Fungolab†; Glicodin; Glycon; Glyteol Balsamico†; Hebrin; Ikaflux; Iodesin; Iodetal; Iodex com Salicilato de Metila; KI-Expectorante; Micotiazol; MM Expectorante; *Canad.*: Herba Tone†; Iode†; ratio-Theo-Bronc; Theraplex P†; *Chile*: Paralymphine; *Cz.*: Jodthyrox; *Fr.*: Femibion Grossesse; Folio; Nitrol†; Sel D; *Ger.*: Adelheid-Jodquelle, Tolzer; Jodthyrox; L-Thyrox Jod†; Lento Nit K; Thyronajod; *Gr.*: Iodocollyre; Tentil; Vitreolent; *Hong Kong*: Duraprep†; Vitreolent†; *India*: Anofer; Arofil; Calodin; Caracsol; Carbosyl; Carbosyl; Catarest; Cato-Bell†; Contrastin; Cureg; Dordent; Elferri Plus; Elixir Efelin; Ethnorub; Fejet-OD; Fejet; Icee; Ioprep; Me-Fresh Gum Paint; Multimix; Oxi-Red; *Indon.*: Calmin-AF; Feritrin; Vitachol; *Israel*: Iodax†; Iodine Tincture; *Ital.*: Antiadiposo; Pacovit; Fertomcidina-U; Jodo Calcio Vitaminico; Linfoiodine†; Natalben; Olimag; Polijodurato; Rubjovit; *Malaysia*: Bio-Cal; Hyiodine; *Mex.*: Calciyodina; Iodex Clasico; Jarabe de Rabano Yodado; *Pol.*: Jodthyrox; *Rus.*: Antioxycaps with Iodine (Антиоксикапс с Йодом); Iodocomb (Йодокомб); Jodthyrox (Йодтирокс); Neo-Anusol (Нео-анузол); Solutan (Солутан)†; Thyreocomb (Тиреокомб); *S.Afr.*: SB Blood Purifying Mixture†; *Singapore*: Chitosano; Shine Bio-Cal; Vitreolent; *Spain*: Adiod; Audionet†; Callicida Rojo†; Depurativo Richelet†; Natifar; Natimed; Nitroina; Yodocefol; Yoduk Complex; Yofolvit; *Switz.*: Radix†; Vitreolent; *Thai.*: Cenamin; Tincture Sahakarn; Tr Iodine Sahakarn; *Turk.*: Broksin; Eupnase; Fenasthma; Fenastma; Neo Sedeks; *UK*: Estroven; Nasciodine; TCP; *Ukr.*: Femibion 400 (Фемибион 400); Femibion 800 (Фемибион 800); Folio (Фолио); Prostalin (Простагин); Stifimol (Стифимол); Vimifor Multivitamin with Beta-Carotene (Вимифор Мультивитамин 3 Бета-каротином)†; Yodofol (Йодофол); *USA*: Elixophyllin-KI; Iodex with Methyl Salicylate; KIE; One A Day Vitacraves; ORA5; Pediacof; Pediruss Cough; Phylorinol; Quadrinal; REQ49 +; *Venez.*: Iodex con Salicilato de Metilo.

Homoeopathic Preparations. *Austral.*: Childrens Runny Nose Relief; Hay Fever; Respatona Nasal Spray Decongestant; *Austria*: Erbiode Haarvital; Famulan; Gentos; Globuli gegen Husten Nr 2; Otovowen; *Canad.*: C-Plus; Calnor†; Complete Flu Care 4 Kids†; Homeo-Form S†; Hylands Flu; Hylands Formula F; Itires; Osteel†; Rhinar†; Sore Throat L39†; Urarthone†; Weight Control; *Chile*: Formula II Especial; Fucus Especial; *Fr.*: Abbe Chaupitre no 48†; Abbe Chaupitre no 91†; Arthro-Drainol; Badiaga Complexe No 47; Boripharm No 31; Dolistamine†; Iodum Complexe No 118; Kalium Iodatum Complexe No 84†; Mercurius Solubilis Complexe No 39; Urarthone; Urtica Complexe No 82†; Zincum Cyanidum Complexe No 101†; *Ger.*: Arte-cyl Ho-Len-Complex; Asthmavowen-N†; Bronchosyx comp; Drufusan N†; Febro-cyl L Ho-Len-Complex; Girheulit HM†; Girheulit HOM; Hewethyreon N; Infekt-Komplex L Ho-Fu-Complex; Lymphaden Lymphdrusentabletten; Neuri-cyl N Ho-Len-Complex; Otovowen; Phonix Thuja-Lachesis spag; Pulmo Bronchial-complex; Pulmo-cyl Ho-Len-Complex; Rufebran allergo†; Thuja N Oligoplex†; Thuja WA Oligoplex; *Hung.*: Gentos; Osteoheel; *Neth.*: Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Nisyspray; *Rus.*: Berberis Comp (Барбарис Комп); Famulan (Фамулан); Gentos (Гентос); *Switz.*: Osteoheel; Regenaplex Nr. 21e; Regenaplex Nr. 24c; *Ukr.*: Arsenic Comp Iov-Diabet (Арсеник Комп Иов-Диабет); Gentos (Гентос).

Pharmacopoeial Preparations

BP 2014: Alcoholic Iodine Solution; Aqueous Iodine Oral Solution; Potassium Iodate Tablets; Sodium Iodide Injection;

BPC 1968: Compound Iodine Paint;

USP 36: Iodine Tincture; Iodine Topical Solution; Minerals Capsules; Minerals Tablets; 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; Potassium Iodide Delayed-release Tablets; Potassium Iodide Oral Solution; Potassium Iodide Tablets; Strong Iodine Solution; Strong Iodine Tincture; Trace Elements Injection; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Levothyroxine Sodium *(BANM, rINN)*

Levothyroxin-Natrium; Levothyroxin sodná sůl hydrát; Lévothyroxine sodique; Levothyroxinnatrium; Levothyroxinum Natricum; Levothyroxinum Natricum Hydricum; Levotiroksin Sodyum; Levotiroksino natrio druska; Levotiroxina sódica; Levotiroxin-nátrium; Levotyroksiininatrium; Levotyroxinnatrium; Lewotyroksyna sodowa; L-Thyroxine Sodium; Thyroxine Sodium; Thyroxinum Natricum; Tirossina; Tiroxina Sodica; Левотироксин Натрий; 3,5,3',5'-Tétra-iodo-L-thyronine Sodium.

Sodium 4-*O*-(4-hydroxy-3,5-di-iodophenyl)-3,5-di-iodo-L-tyrosine hydrate.

$C_{15}H_{10}I_4NNaO_4.xH_2O$=798.9 (anhydrous)

CAS — 51-48-9 (levothyroxine); 55-03-8 (anhydrous levothyroxine sodium); 25416-65-3 (levothyroxine sodium, hydrate); 8065-29-0 (liotrix).

ATC — H03AA01.

ATC Vet — QH03AA01.

UNII — 054I36CPMN (anhydrous levothyroxine sodium); 9J7655329G (levothyroxine sodium); YW8HU0N26X (liotrix).

NOTE. The abbreviation T_4 is often used for endogenous thyroxine in medical and biochemical reports. Liotrix is *USAN* for a mixture of liothyronine sodium with levothyroxine sodium.

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

Int. includes the anhydrous form.

Ph. Eur. 8: (Levothyroxine Sodium). An almost white or slightly brownish-yellow, fine, slightly hygroscopic, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Levothyroxine Sodium). The sodium salt of L-3,3',5,5'-tetraiodothyronine. A light yellow to buff-coloured, odourless, hygroscopic, powder. It may assume a slight pink colour on exposure to light. Soluble 1 in 700 of water and 1 in 300 of alcohol; insoluble in acetone, in chloroform, and in ether; soluble in solutions of alkali hydroxides and in hot solutions of alkali carbonates. pH of a saturated solution in water is about 8.9. Store in airtight containers. Protect from light.

Uses and Administration

Levothyroxine is a thyroid hormone (see p. 2332.1 for a description of the endogenous hormones) used as replacement therapy in the treatment of hypothyroidism (p. 2333.3). It is given in conditions such as diffuse non-toxic goitre (see Goitre and Thyroid Nodules, p. 2332.1) and Hashimoto's thyroiditis (see Hypothyroidism, p. 2333.3) to suppress the secretion of thyroid-stimulating hormone (TSH) and hence prevent or reverse enlargement of the thyroid gland. Levothyroxine is also used to suppress TSH production in the treatment of thyroid carcinoma (p. 716.1) and as a diagnostic agent for the differential diagnosis of hyperthyroidism. It is given with antithyroid drugs in the blocking-replacement regimen for the management of hyperthyroidism (p. 2332.2).

The peak therapeutic effect of regular oral levothyroxine may not be achieved for several weeks and there is a slow response to changes in dosage. Similarly, effects may persist for several weeks after withdrawal. Levothyroxine is given as the sodium salt in a single daily dose. Its absorption can be irregular and it is probably best taken on an empty stomach, usually before breakfast.

The dose of levothyroxine sodium for the treatment of any thyroid disorder should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly.

In hypothyroidism an initial oral dose of 50 to 100 micrograms of levothyroxine sodium daily may be increased by 25 to 50 micrograms at intervals of about 3 to 4 weeks until the thyroid deficiency is corrected and a maintenance dose is established. The maintenance dose is usually between 100 and 200 micrograms daily.

In patients over 50 years, in those with cardiac disease, or in those with severe hypothyroidism of long standing, treatment should be introduced more gradually: an initial dose of 12.5 to 50 micrograms daily increased by increments of 12.5 to 25 micrograms at intervals ranging from about 2 to 8 weeks may be appropriate, to usual maintenance doses between 50 and 200 micrograms daily.

For the use of levothyroxine in children, see below.

Levothyroxine sodium may be given by intravenous injection. It has also been given intramuscularly. In myxoedema (hypothyroid) coma a dose of 300 to 500 micrograms by intravenous injection may be given initially. Further doses of 50 to 100 micrograms may be given daily until the patient is clinically stable and can tolerate oral doses.

Dextrothyroxine, the D-isomer of levothyroxine, has lipid regulating properties and has been used in the management of hypercholesterolaemia, but its use is severely limited by cardiotoxicity; it has only weak thyroid hormone activity.

General references.

1. Mandel SJ, *et al.* Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med* 1993; **119:** 492–502.
2. Toft AD. Thyroxine therapy. *N Engl J Med* 1994; **331:** 174–80. Correction. *ibid.*; 1035.
3. Escobar-Morreale HF, *et al.* Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. *J Clin Endocrinol Metab* 2005; **90:** 4946–54.

Administration. *BIOEQUIVALENCE.* There has been controversy over the bioequivalence or otherwise of different brands of levothyroxine. Most studies and reports have come from the USA and results may have depended to some extent on the particular brands compared. Formulations may also have changed which makes comparison of results difficult. One study[1] concluded that 2 generic levothyroxine products were bioequivalent and interchangeable with 2 branded products.

In 2004 the FDA issued guidance on the bioequivalence of several levothyroxine products on the US market but this was heavily criticised in a joint statement by several American professional societies.[2] In response, these societies recommended to physicians that patients should be maintained on the same brand of levothyroxine and if the brand were changed then the patient's serum TSH should be retested and the dosage of levothyroxine re-titrated as necessary. Similar advice was issued in New Zealand in 2008, when a change in formulation within the same brand of levothyroxine resulted in a higher incidence of adverse drug reaction reporting.[3]

1. Dong BJ, *et al.* Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA* 1997; **277:** 1205–13.
2. American Association of Clinical Endocrinologists, The Endocrine Society, and American Thyroid Association. Joint position statement on the use and interchangeability of thyroxine products. Available at: https://www.aace.com/sites/default/files/AACE-TES-ATA-ThyroxineProducts.pdf (accessed 02/08/11) See also American Thyroid Association, The Endocrine Society, and American Association of Clinical Endocrinologists. Joint Statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. *Thyroid* 2004; **14:** 486.
3. New Zealand Medicines and Medical Devices Safety Authority. Eltroxin formulation change - Monitor patients and adjust dosing if necessary (issued 26 June, 2008). Available at: http://www.medsafe.govt.nz/hot/alerts/eltroxin.asp (accessed 12/12/08)

ROUTE. Intra-amniotic injection of levothyroxine has been used to treat fetal goitrous hypothyroidism.[1,2] In one case, diagnosis was made at 36 weeks of gestation, and two doses of 300 micrograms of levothyroxine were injected into the maternal amniotic fluid between 37 and 38 weeks of gestation. Mild tachypnoea and an enlarged thyroid gland were noted in the neonate, who also required a further 2 weeks of oral levothyroxine for persistent neonatal hypothyroidism.[1] In a retrospective study of 12 infants, prenatal treatment varied widely in terms of levothyroxine dosage; intra-amniotic doses of between 200 to 800 micrograms were given. No adverse effects were seen, but all infants were hypothyroid at birth. The authors concluded that, while the method is feasible and safe and probably effective in decreasing goitre size, no guidelines can be developed until further studies are done.[2]

1. Miyata I, *et al.* Successful intrauterine therapy for fetal goitrous hypothyroidism during late gestation. *Endocr J* 2007; **54:** 813–17.
2. Ribault V, *et al.* French Fetal Goiter Study Group. Experience with intraamniotic thyroxine treatment in nonimmune fetal goitrous hypothyroidism in 12 cases. *J Clin Endocrinol Metab* 2009; **94:** 3731–9.

TIMING. Although levothyroxine is usually taken in the morning on an empty stomach for hypothyroidism (see Uses and Administration, above), a controlled study[1] found improved thyroid hormone concentrations when the dose was given at night; no significant changes in patients' plasma lipid concentrations or quality of life were seen.

The recommendation that levothyroxine be taken on an empty stomach has also been questioned; in particular, on the grounds that it may cause problems with adherence in infants and children. US expert bodies have suggested that consistent administration with regard to timing and meals is more important than the presence or absence of food (although giving it with iron or calcium should be avoided). In addition, soya-based infant formulas may impair absorption of levothyroxine, and frequent testing may be needed, particularly when there are changes in formula.[2]

1. Bolk N, *et al.* Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. *Arch Intern Med* 2010; **170:** 1996–2003.
2. Zeitler P, Solberg P. Pharmacy and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Food and levothyroxine administration in infants and children. *J Pediatr* 2010; **157:** 13–14.

Administration in children. It is especially important that children with hypothyroidism have their dosage individualised and treatment monitored. In the UK, the *BNFC* recommends the following oral doses of levothyroxine sodium:

- neonates: 10 to 15 micrograms/kg once daily (to a maximum of 50 micrograms daily) initially, adjusted in steps of 5 micrograms/kg every 2 weeks or as needed, to a usual maintenance dose of 20 to 50 micrograms daily
- children aged 1 month to 2 years: 5 micrograms/kg once daily (to a maximum of 50 micrograms daily) initially, adjusted in steps of 10 to 25 micrograms daily every 2 to 4 weeks until metabolism is normalised, to a usual maintenance dose of 25 to 75 micrograms daily
- children aged 2 to 12 years: 50 micrograms once daily initially, adjusted in steps of 25 micrograms daily every 2 to 4 weeks until metabolism is normalised, to a usual maintenance dose of 75 to 100 micrograms daily
- children aged 12 to 18 years: 50 micrograms once daily initially, then adjusted as for adults, see above

For discussion of the timing of dosage in infants and children see above.

Cardiomyopathies. Management of dilated cardiomyopathy (p. 1261.3) usually involves conventional therapy for heart failure, but a small study has reported benefit from short-term use of oral levothyroxine.[1] Levothyroxine was well tolerated but thyroid-stimulating hormone levels were reduced, which might limit long-term therapy. Simi-

lar results have been reported with short-term intravenous liothyronine.[2]

1. Moruzzi P, *et al.* Medium-term effectiveness of L-thyroxine treatment in idiopathic dilated cardiomyopathy. *Am J Med* 1996; **101**: 461–7.
2. Pingitore A, *et al.* Acute effects of triiodothyronine (T_3) replacement therapy in patients with chronic heart failure and low-T_3 syndrome: a randomized, placebo-controlled study. *J Clin Endocrinol Metab* 2008; **93**: 1351–8.

Depression. While thyroid hormones may increase the activity of tricyclic antidepressants (see Thyroid Hormones, under Interactions of Amitriptyline, p. 407.2), the benefits in the augmentation treatment of depression (p. 398.1) are debatable. A meta-analysis[1] of 8 studies involving 292 patients with refractory depression treated with liothyronine in addition to tricyclic antidepressants indicated that such therapy was effective in a subgroup of cases but that the small number of patients studied made additional placebo-controlled data desirable.

In non-refractory depression a meta-analysis[2] also indicated a benefit when liothyronine was added to tricyclic antidepressants although it was acknowledged that many of the studies were old with methodological limitations. Subsequent studies have shown conflicting results. A controlled study of liothyronine with paroxetine could not confirm any advantage of additive therapy,[3] whereas another[4] found an improvement in response and remission when liothyronine was added to sertraline therapy. The authors of the latter study commented upon the conflicting results with the previous study, highlighting the difference in the proportion of patients with chronic depression; response to the combination of sertraline plus liothyronine was related to the duration of the current depressive episode, with duration being significantly shorter in those who responded.[4]

1. Aronson R, *et al.* Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Arch Gen Psychiatry* 1996; **53**: 842–8.
2. Altshuler LL, *et al.* Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry* 2001; **158**: 1617–22.
3. Appelhof BC, *et al.* Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. *J Clin Endocrinol Metab* 2004; **89**: 6271–6.
4. Cooper-Kazaz R, *et al.* Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 2007; **64**: 679–88.

Obesity. Thyroid drugs have been tried in the treatment of obesity (p. 2315.1) in euthyroid patients, but they produce only temporary weight loss, mainly of lean body-mass, and can produce serious adverse effects, especially cardiac complications.[1] Hypothyroidism has also been reported[2] when these drugs were withdrawn from previously euthyroid patients being treated for simple obesity. Levothyroxine appears to have been abused by some athletes to promote weight loss;[3] liothyronine has been abused similarly.[4] A systematic review[5] concluded that data were inconclusive as to the efficacy of thyroid hormone therapy for treating obesity. However, data supported the suggestion that thyroid hormone therapy induced subclinical hyperthyroidism in obese subjects, and therapy was not recommended in euthyroid patients.

1. Rivlin RS. Therapy of obesity with hormones. *N Engl J Med* 1975; **292**: 26–9.
2. Dornhorst A, *et al.* Possible iatrogenic hypothyroidism. *Lancet* 1981; **i**: 52.
3. MacAuley D. Drugs in sport. *BMJ* 1996; **313**: 211–15.
4. Hartung B, *et al.* Lethal thyroid storm after uncontrolled intake of liothyronine in order to lose weight. *Int J Legal Med* 2010; **124**: 637–40.
5. Kaptein EM, *et al.* Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. *J Clin Endocrinol Metab* 2009; **94**: 3663–75.

Thyroid autoantibodies. A systematic review and meta-analysis[1] indicated that the presence of thyroid autoantibodies in women with normal thyroid function was strongly associated with an increased risk of miscarriage and preterm birth. There was some evidence suggesting that low-dose levothyroxine treatment during pregnancy might reduce these risks,[1] but further studies were needed and a prospective double-blind study (the TABLET study) was planned.[2]

1. Thangaratinam S, *et al.* Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ* 2011; **342**: d2616.
2. Negro R, Stagnaro-Green A. Thyroid autoantibodies, preterm birth, and miscarriage. *BMJ* 2011; **342**: 1035–6.

Urticaria. There is some suggestion that chronic urticaria (p. 1689.2) may be associated with thyroid autoimmunity and that treatment with thyroid hormones may result in clinical remission.[1] In one study, a nine-year-old boy was successfully treated for chronic urticaria with levothyroxine therapy at doses of 50 to 100 micrograms daily.[2] The authors advised screening for thyroid function and anti-thyroid microsomal antibodies in cases of chronic urticaria as these patients may benefit from thyroid hormone therapy. A small investigative study concluded that treatment with levothyroxine sodium (in hypothyroid patients) or antithyroid drugs (in patients with Graves' disease) is of benefit in patients with severe chronic urticaria associated with thyroid autoimmunity.[3] A review[4] concluded that about 25% of patients with chronic idiopathic urticaria have serological evidence of thyroid autoantibodies, and that screening for thyroid autoimmunity may be useful in these patients. While acknowledging anecdotal reports of levothyroxine's efficacy in ameliorating urticaria, the authors concluded that definitive data were needed before any recommendation could be made for its use.

1. Rumbyrt JS, *et al.* Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995; **96**: 901–5.
2. Dreyfus DH, *et al.* Steroid-resistant chronic urticaria associated with anti-thyroid microsomal antibodies in a nine-year-old boy. *J Pediatr* 1996; **128**: 576–8.
3. Gaig P, *et al.* Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity. *J Investig Allergol Clin Immunol* 2000; **10**: 342–5.
4. Bagnasco M, *et al.* Urticaria and thyroid autoimmunity. *Thyroid* 2011; **21**: 401–10.

Adverse Effects and Treatment

The adverse effects of levothyroxine are generally associated with excessive dosage and correspond to symptoms of hyperthyroidism. They may include tachycardia, palpitations, cardiac arrhythmias, increase in blood pressure, anginal pain, headache, restlessness, excitability, insomnia, tremors, muscle weakness and cramps, heat intolerance, sweating, flushing, fever, weight loss, menstrual irregularities, diarrhoea, and vomiting. These adverse reactions usually disappear after dosage reduction or temporary withdrawal of treatment. Elevations in liver function tests and decreased bone mineral density have been reported. Hypersensitivity reactions can occur. Thyroid storm has occasionally been reported after massive or chronic intoxication and convulsions, cardiac arrhythmias, heart failure, coma, and death have occurred.

Treatment of overdose is usually symptomatic and supportive; propranolol may be useful in controlling the symptoms of sympathetic overactivity. The UK National Poisons Information Service states that the benefit of gastric decontamination in acute overdosage of levothyroxine is uncertain; oral activated charcoal may be considered for an adult or child presenting within 1 hour of ingestion of doses over 100 micrograms/kg. Levothyroxine overdosage requires an extended follow-up period as symptoms may be delayed for up to 6 days due to the gradual peripheral conversion of levothyroxine to tri-iodothyronine; glucocorticoids may be given to inhibit this conversion.

Carcinogenicity. An association between the use of thyroid hormones and an increased risk of breast cancer in women has been proposed,[1] but a further analysis of the data did not confirm such an association,[2] and nor did later studies.[3–5]

1. Kapdi CC, Wolfe JN. Breast cancer. Relationship to thyroid supplements for hypothyroidism. *JAMA* 1976; **236**: 1124–7.
2. Mustacchi P, Greenspan F. Thyroid supplementation for hypothyroidism. An iatrogenic cause of breast cancer? *JAMA* 1977; **237**: 1446–7.
3. Wallace RB, *et al.* Thyroid hormone use in patients with breast cancer. Absence of an association. *JAMA* 1978; **239**: 958.
4. Shapiro S, *et al.* Use of thyroid supplements in relation to the risk of breast cancer. *JAMA* 1980; **244**: 1685–7.
5. Hoffman DA, *et al.* Breast cancer in hypothyroid women using thyroid supplements. *JAMA* 1984; **251**: 616–19.

Effects on the bones. Hyperthyroidism is a known risk factor for osteoporosis and theoretically thyroid hormone therapy may also be a risk factor. A review of over 3000 patients from 63 studies summarised the available evidence on the association of levothyroxine and bone mineral density.[1] It was stressed that current findings were complex and confusing and poor methodological quality made comparison of results difficult. However, it was concluded that neither dose of levothyroxine nor duration of therapy had any relationship with bone mineral density (BMD): 31 studies showed no overall effect of levothyroxine, 23 studies provided partial negative and/or positive effects, while 9 showed overall negative effects. For postmenopausal women, particularly those with a history of hyperthyroidism, the review[1] recommended monitoring of thyroid hormone levels to avoid clinical hyperthyroidism, and screening for risk factors of osteoporosis; if warranted, bone densitometry, and appropriate management of any decline in BMD, should be used.

A retrospective case-control study[2] found a significant association between current levothyroxine use and increased risk of fracture in people over 70 years of age, with a strong dose-response relationship. An increased risk remained in those who had stopped levothyroxine therapy within the previous 6 months.

1. Schneider R, Reiners C. The effect of levothyroxine therapy on bone mineral density: a systematic review of the literature. *Exp Clin Endocrinol Diabetes* 2003; **111**: 455–70.
2. Turner MR, *et al.* Levothyroxine dose and risk of fractures in older adults: nested case-control study. *BMJ* 2011; **342**: d2238.

Effects on the muscles. A Taiwanese female with previous normal thyroid function developed thyrotoxic periodic paralysis (TPP) affecting the limbs after abusing levothyroxine, 100 micrograms twice daily for 2 weeks, in order to lose weight.[1] The attack subsided after treatment with intravenous potassium and withdrawal of the levothyroxine. Although TPP is a condition most commonly seen in patients of South Asian origin there is a report of TPP precipitated by excessive levothyroxine replacement therapy in a Caucasian patient with panhypopituitarism.[2]

1. Chen YC, *et al.* Thyrotoxic periodic paralysis in a patient abusing thyroxine for weight reduction. *Ren Fail* 2001; **23**: 139–42.
2. Hannon MJ, *et al.* Thyrotoxic periodic paralysis due to excessive L-thyroxine replacement in a Caucasian man. *Ann Clin Biochem* 2009; **46**: 423–5.

Effects on the nervous system. Two children aged 8 and 11 years developed pseudotumor cerebri (benign intracranial hypertension) shortly after starting levothyroxine for hypothyroidism.[1] There have been further reports on individual children[2–4] and infants.[5]

Partial complex status epilepticus, with confusion, agitation, and continuous myoclonic jerks in the left side of the face and left hand, was seen in a hypothyroid patient with Turner's syndrome who was receiving levothyroxine for myxoedema coma.[6] The condition responded to anticonvulsants; the patient subsequently remained seizure-free on a reduced dose of levothyroxine and concomitant phenytoin.

A 35-year-old woman with auto-immune thyroiditis, who increased her levothyroxine dosage to 300 micrograms daily in an attempt to lose weight, lost 20 kg over the next 6 months but developed incapacitating choreoathetosis.[7] However, all her symptoms had resolved a week after reducing her dosage back to 100 micrograms daily.

1. Van Dop C, *et al.* Pseudotumor cerebri associated with initiation of levothyroxine therapy for juvenile hypothyroidism. *N Engl J Med* 1983; **308**: 1076–80.
2. McVie R. Pseudotumor cerebri and thyroid-replacement therapy. *N Engl J Med* 1983; **309**: 731.
3. Hymes LC, *et al.* Pseudotumor cerebri and thyroid-replacement therapy. *N Engl J Med* 1983; **309**: 732.
4. Strickler C, Pilon AF. Presumed levothyroxine-induced pseudotumor cerebri in a pediatric patient being treated for congenital hypothyroidism. *Clin Ophthalmol* 2007; **1**: 545–9.
5. Raghavan S, *et al.* Pseudotumor cerebri in an infant after L-thyroxine therapy for transient neonatal hypothyroidism. *J Pediatr* 1997; **130**: 478–80.
6. Duane J, *et al.* Thyroxine-induced partial complex status epilepticus. *Ann Pharmacother* 1993; **27**: 1139.
7. Kondziella D, *et al.* Choreathetosis due to abuse of levothyroxine. *J Neurol* 2009; **256**: 2106–8.

Hypersensitivity. A hypersensitivity reaction (fever, eosinophilia, and liver dysfunction) was reported[1] in a 63-year-old hypothyroid woman with Hashimoto's thyroiditis during treatment with liothyronine or levothyroxine. Symptoms disappeared when the drugs were stopped. After an interval of 4 months liothyronine was gradually reintroduced without adverse effect.

Urticaria and angioedema have been described in a patient who received thyroid and levothyroxine.[2] In a further case similar reactions were attributed to the presence of sunset yellow as colouring agent in the proprietary levothyroxine preparation.[3]

1. Shibata H, *et al.* Hypersensitivity caused by synthetic thyroid hormones in a hypothyroid patient with Hashimoto's thyroiditis. *Arch Intern Med* 1986; **146**: 1624–5.
2. Pandya AG, *et al.* Chronic urticaria associated with exogenous thyroid use. *Arch Dermatol* 1990; **126**: 1238–9.
3. Lévesque H, *et al.* Reporting adverse drug reactions by proprietary name. *Lancet* 1991; **338**: 393.

Overdosage. In overdosage with thyroid drugs aggressive therapy is not normally justified in asymptomatic patients, although various regimens have been tried in large overdosage.

Massive overdoses of levothyroxine and liothyronine (up to 1000 times the normal dose over 2 to 12 days) have been described in small numbers of patients.[1–8] Symptoms of thyrotoxicosis can occur within the first 6 hours after ingestion of liothyronine but can be delayed for 2 to 5 days after levothyroxine, due to the time taken for metabolic conversion to liothyronine. Symptoms of thyrotoxicosis that have been reported include fever, arrhythmias, tachycardia, increased blood pressure, confusion, agitation, neurological complications, and coma.[1,2,5] Treatment of overdosage includes consideration of the use of activated charcoal and a beta blocker such as propranolol or metoprolol to treat tachyarrhythmia.[2,4,5] In most cases serious toxicity does not occur and patients recover with supportive therapy. Diuresis and haemodialysis do not enhance elimination because thyroid hormones are highly protein bound. It has also been concluded that plasmapheresis and haemoperfusion provide no significant clinical benefit.[4,6]

1. Kulig K, *et al.* Levothyroxine overdosage associated with seizures in a young child. *JAMA* 1985; **254**: 2109–10.
2. Binimelis J, *et al.* Massive thyroxine intoxication: evaluation of plasma extraction. *Intensive Care Med* 1987; **13**: 33–8.
3. Golightly LK, *et al.* Clinical effects of accidental levothyroxine ingestion in children. *Am J Dis Child* 1987; **141**: 1025–7.

4. Henderson A, *et al.* Lack of efficacy of plasmapheresis in a patient overdosed with thyroxine. *Anaesth Intensive Care* 1994; 22: 463–4.
5. Hack JB, *et al.* Severe symptoms following a massive intentional L-thyroxine ingestion. *Vet Hum Toxicol* 1999; 41: 323–6.
6. Solá E, *et al.* Massive triiodothyronine intoxication: efficacy of hemoperfusion? *Thyroid* 2002; 7: 637–40.
7. Tsutsaeva BT, *et al.* Seizure in a child after an acute ingestion of levothyroxine. *Pediatr Emerg Care* 2005; 21: 857–9.
8. Ho J, *et al.* Massive levothyroxine ingestion in a pediatric patient: case report and discussion. *CJEM* 2011; 13: 165–8.

Precautions

Levothyroxine is contra-indicated in untreated hyperthyroidism. It has a narrow therapeutic index and should be used with extreme caution in patients with cardiovascular disorders including angina, heart failure, myocardial infarction, and hypertension; lower initial doses, smaller increments, and longer intervals between increases should be used as necessary. An ECG performed before starting treatment with levothyroxine may help to distinguish underlying myocardial ischaemia from changes induced by hypothyroidism. Levothyroxine should also be introduced very gradually in elderly patients and those with long-standing hypothyroidism to avoid any sudden increase in metabolic demands. It should not be given to patients with adrenal insufficiency without adequate corticosteroid cover otherwise the thyroid replacement therapy might precipitate an acute adrenal crisis. Care is also required when levothyroxine is given to patients with diabetes mellitus or diabetes insipidus. Thyroid hormones may affect the seizure threshold and care is needed when levothyroxine is given to patients with epilepsy.

Tests of thyroid function are subject to alteration by some nonthyroidal clinical conditions and by many drugs, some of which are mentioned under Interactions, below.

Abuse. For mention of abuse of levothyroxine by athletes for weight loss see Obesity, under Uses and Administration, p. 2340.1. For reference to periodic paralysis in a woman abusing levothyroxine as a slimming aid, see under Effects on the Muscles, p. 2340.2.

Adrenocortical insufficiency. Thyroid-hormone replacement without additional corticosteroids may precipitate acute adrenocortical insufficiency in patients with impaired adrenocortical function, including those with subclinical or unrecognised adrenocortical disease.[1] Prompt diagnosis and replacement of corticosteroids can prevent the development of a potentially fatal crisis. It has been pointed out that a raised concentration of thyroid-stimulating-hormone alone may not necessarily imply hypothyroidism in patients with chronic adrenocortical insufficiency.[2] Even confirmed hypothyroidism in these patients may not be permanent.

1. Fonseca V, *et al.* Acute adrenal crisis precipitated by thyroxine. *BMJ* 1986; 292: 1185–6.
2. Davis J, Sheppard M. Acute adrenal crisis precipitated by thyroxine. *BMJ* 1986; 292: 1595.

Anaemia. Four patients with iron deficiency anaemia and primary hypothyroidism developed palpitations and restlessness on treatment with levothyroxine sodium, and the drug had to be stopped. Upon correction of the anaemia with ferrous sulfate, all were able to tolerate levothyroxine therapy.[1] For a warning that ferrous sulfate reduces absorption of levothyroxine from the gastrointestinal tract, see Iron Salts under Interactions, p. 2342.1.

1. Shakir KMM, *et al.* Anemia: a cause of intolerance to thyroxine sodium. *Mayo Clin Proc* 2000; 75: 189–92.

Breast feeding. Minimal amounts of thyroid hormones are distributed into breast milk. The last available guidance from the American Academy of Pediatrics noted that no effects had been seen in breast-fed infants whose mothers were taking levothyroxine and as such considered its use to be usually compatible with breast feeding.[1]

Although levothyroxine in breast milk will be insufficient to treat any hypothyroidism in the suckling newborn, it has been suggested that it may mask detection of any hypothyroidism in such a neonate.[2] However, the *BNF* considers that the amounts involved are too small to affect tests for neonatal hypothyroidism.

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 18/05/05)
2. Anonymous. Can a woman on thyroxine safely breast-feed her baby? *BMJ* 1977; 2: 1589.

Cardiovascular disorders. There is a complex relationship between the heart and thyroid.[1] Cardiovascular abnormalities may be associated with hypothyroidism as well as with levothyroxine replacement therapy, hence the need for caution.

1. Gammage M, Franklyn J. Hypothyroidism, thyroxine treatment, and the heart. *Heart* 1997; 77: 189–90.

Myasthenia. Thyroid hormones may occasionally precipitate or exacerbate a pre-existing myasthenic syndrome.[1,2]

1. Mastaglia FL. Adverse effects of drugs on muscle. *Drugs* 1982; 24: 304–21.
2. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; 26: 124–47.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levothyroxine 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. Most authorities consider that thyroid hormones do not readily cross the placenta. Placental transfer has been reported,[1] but in amounts so limited that a mother with physiological concentrations of thyroxine and tri-iodothyronine would not provide normal thyroid hormone concentrations to a fetus with congenital hypothyroidism.[2-4]

Levothyroxine requirements increase in hypothyroid women during early pregnancy. A small study involving 20 pregnancies found that the dose requirement rose from the sixth to the sixteenth week of gestation before reaching a plateau; a mean dose increase of nearly 50% was eventually required in 17 cases.[5] The authors recommended that all hypothyroid women should have their levothyroxine dose increased by 30% as soon as pregnancy was confirmed, to avoid any risk of an initial period of hypothyroxinaemia before the first obstetric visit. Thereafter, dosage should be adjusted according to serum-thyrotropin concentrations. See also under Hypothyroidism, p. 2333.3.

For mention of the possible value of levothyroxine treatment in reducing miscarriage and premature births in euthyroid women with thyroid autoantibodies, see Thyroid Autoantibodies under Uses, p. 2340.1.

1. Vulsma T, *et al.* Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med* 1989; 321: 13–16.
2. Sack J, *et al.* Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; 321: 1549–50.
3. Bachrach LK, Burrow GN. Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; 321: 1549.
4. Vulsma T, *et al.* Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; 321: 1550.
5. Alexander EK, *et al.* Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004; 351: 241–9.

Interactions

References.

1. Takahashi N, *et al.* Effect of thyroid hormone on the activity of CYP3A enzyme in humans. *J Clin Pharmacol* 2010; 50: 88–93.

Antiarrhythmics. *Amiodarone*[1] may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine with a rise in the concentration of inactive reverse tri-iodothyronine.

1. Hershman JM, *et al.* Thyroxine and triiodothyronine kinetics in cardiac patients taking amiodarone. *Acta Endocrinol (Copenh)* 1986; 111: 193–9.

Antibacterials. Enzyme induction by *rifampicin*[1,2] enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones.

Two patients with previously stable thyroid function while receiving levothyroxine were found to have developed hypothyroidism 3 to 4 weeks after starting oral treatment with *ciprofloxacin*.[3] In one patient increasing the dose of levothyroxine was ineffective and thyroid function only returned to normal after ciprofloxacin was withdrawn. In the other patient, giving the drugs 6 hours apart was sufficient to overcome the interaction.

1. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* 1983; 15: 71–6.
2. Nolan SR, *et al.* Interaction between rifampin and levothyroxine. *South Med J* 1999; 92: 529–31.
3. Cooper JG, *et al.* Ciprofloxacin interacts with thyroid replacement therapy. *BMJ* 2005; 330: 1002.

Anticoagulants. Thyroid hormones enhance the effects of *oral anticoagulants* (see under the interactions of Warfarin, p. 1535.2). Patients on anticoagulant therapy therefore require careful monitoring when treatment with thyroid drugs is started or altered as the oral anticoagulant dose may need to be adjusted.

Antidepressants. Some drugs such as *lithium* act directly on the thyroid gland and inhibit the release of thyroid hormones leading to clinical hypothyroidism.[1]

The effects of levothyroxine in hypothyroid patients may be decreased by use with *sertraline*, and the dose of levothyroxine may need to be increased.[2]

For the effects of thyroid hormones on *tricyclic antidepressants* see under Amitriptyline, p. 407.2.

1. Ramsay I. Drugs and non-thyroid induced changes in thyroid function tests. *Postgrad Med J* 1985; 61: 375–7.
2. McCowen KC, *et al.* Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *N Engl J Med* 1997; 337: 1010–11.

Antidiabetics. As thyroid status influences metabolic activity and most body systems, correction of hypothyroidism may affect other disease states and dosage of any drug treatment. In hypothyroid diabetics for instance, starting thyroid replacement therapy may increase their *insulin* or *oral hypoglycaemic* requirements.[1]

1. Refetoff S. Thyroid hormone therapy. *Med Clin North Am* 1975; 59: 1147–62.

Antiepileptics. Enzyme induction by drugs such as *carbamazepine*,[1,2] *phenytoin*,[2,3] or *barbiturates*[4] enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones. Therefore, patients on thyroid replacement therapy may require an increase in their dose of thyroid hormone if these drugs are also given[5] and a decrease if the enzyme-inducing drug is withdrawn.[6] *Phenytoin*,[3] and *carbamazepine* may reduce protein binding by displacing the thyroid hormones from their plasma-binding sites. As thyroid hormones are highly protein bound, changes in binding might be expected to influence requirements in thyroid replacement therapy, but in practice there is little clinical evidence of any problems except with thyroid-function testing.

1. Connell JMC, *et al.* Changes in circulating thyroid hormones during short-term hepatic enzyme induction with carbamazepine. *Eur J Clin Pharmacol* 1984; 26: 453–6.
2. Larkin JG, *et al.* Thyroid hormone concentrations in epileptic patients. *Eur J Clin Pharmacol* 1989; 36: 213–6.
3. Franklyn JA, *et al.* Measurement of free thyroid hormones in patients on long-term phenytoin therapy. *Eur J Clin Pharmacol* 1984; 26: 633–4.
4. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* 1983; 15: 71–6.
5. Blackshear JL, *et al.* Thyroxine replacement requirements in hypothyroid patients receiving phenytoin. *Ann Intern Med* 1983; 99: 341–2.
6. Hoffbrand BI. Barbiturate/thyroid-hormone interaction. *Lancet* 1979; ii: 903–4.

Antimalarials. Increased thyroid-stimulating hormone concentration has been noted after the use of *chloroquine* with *proguanil* for malaria prophylaxis in a patient stabilised on levothyroxine.[1] Induction of liver enzymes by chloroquine resulting in increased metabolism of levothyroxine was suggested as the mechanism.

1. Munera Y, *et al.* Interaction of thyroxine sodium with antimalarial drugs. *BMJ* 1997; 314: 1593.

Antineoplastics. Eight patients taking levothyroxine, subsequent to thyroidectomy, developed raised concentrations of thyroid-stimulating hormone (TSH) and clinical hypothyroidism when they were given *imatinib*. Increasing the levothyroxine dose reversed hypothyroidism in only 3 patients, but TSH concentrations returned to normal in all patients when imatinib was stopped. In contrast, these effects did not occur in 3 other patients with a normal functioning thyroid. The authors reasoned that imatinib might have stimulated the clearance of thyroxine and tri-iodothyronine by inducing uridine diphosphate glucuronosyltransferases, but evidence is needed to confirm this mechanism. They suggested that the dose of levothyroxine should be at least doubled, with close monitoring of thyroid function, before imatinib is given to patients with hypothyroidism.[1]

1. de Groot JWB, *et al.* Imatinib induces hypothyroidism in patients receiving levothyroxine. *Clin Pharmacol Ther* 2005; 78: 433–8.

Antivirals. There have been reports of interactions between HIV-protease inhibitors and levothyroxine. An increased dose of levothyroxine was necessary with *ritonavir*[1] whereas a decreased dose was needed with *indinavir*.[2]

1. Tseng A, Fletcher D. Interaction between ritonavir and levothyroxine. *AIDS* 1998; 12: 2235–6.
2. Lanzafame M, *et al.* Interaction between levothyroxine and indinavir in a patient with HIV infection. *Infection* 2002; 30: 54–5.

Beta blockers. Studies have indicated that plasma concentrations of *propranolol* are reduced in hyperthyroidism compared with the euthyroid state, probably due to increased clearance[1-4] and hypothyroid patients receiving chronic propranolol therapy have had a reduction in plasma-propranolol concentrations when given levothyroxine treatment.[2]

Propranolol may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine and a rise in the concentration of inactive reverse tri-iodothyronine.[5,6]

1. Feely J, *et al.* Increased clearance of propranolol in thyrotoxicosis. *Ann Intern Med* 1981; 94: 472–4.
2. Feely J, *et al.* Plasma propranolol steady state concentrations in thyroid disorders. *Eur J Clin Pharmacol* 1981; 19: 329–33.
3. Aro A, *et al.* Pharmacokinetics of propranolol and sotalol in hyperthyroidism. *Eur J Clin Pharmacol* 1982; 21: 373–7.
4. Hallengren B, *et al.* Influence of hyperthyroidism on the kinetics of methimazole, propranolol, metoprolol, and atenolol. *Eur J Clin Pharmacol* 1982; 21: 379–84.

5. Chambers JB, *et al.* The effects of propranolol on thyroxine metabolism and triiodothyronines production in man. *J Clin Pharmacol* 1982; 22: 110–16.
6. Wilkins MR, *et al.* Effect of propranolol on thyroid homeostasis of healthy volunteers. *Postgrad Med J* 1985; 61: 391–4.

Cardiac glycosides. Serum-digoxin concentrations appear to be lower in hyperthyroidism and higher in hypothyroidism,[1] which may contribute in part to the observed insensitivity of hyperthyroid patients to *digoxin* therapy,[2] although other mechanisms have been proposed.[3]

1. Croxson MS, Ibbertson HK. Serum digoxin in patients with thyroid disease. *BMJ* 1975; 3: 566–8.
2. Huffman DH, *et al.* Digoxin in hyperthyroidism. *Clin Pharmacol Ther* 1977; 22: 533–8.
3. Lawrence JR, *et al.* Digoxin kinetics in patients with thyroid dysfunction. *Clin Pharmacol Ther* 1977; 22: 7–13.

Chelators and antidotes. *Lanthanum carbonate* reduced the absorption of levothyroxine, an effect that was thought to be due to the lanthanum ion binding with thyroid hormones in the gastrointestinal tract. An interval of at least 2 hours is suggested between taking the 2 drugs.[1] A similar effect has been seen with *sodium polystyrene sulfonate*[2] and sevelamer.[3–5]

1. Weitzman SP, *et al.* Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. *Thyroid* 2009; 19: 77–9.
2. McLean M, *et al.* Cation-exchange resin and inhibition of intestinal absorption of thyroxine. *Lancet* 1993; 341: 1286.
3. Diskin CJ, *et al.* Effect of phosphate binders upon TSH and L-thyroxine dose in patients on thyroid replacement. *Int Urol Nephrol* 2007; 39: 599–602.
4. John-Kalarickal J, *et al.* New medications which decrease levothyroxine absorption. *Thyroid* 2007; 17: 763–5.
5. Arnadottir M, Johannesson AJ. Phosphate binders and timing of levothyroxine administration. *Nephrol Dial Transplant* 2008; 23: 420.

Gastrointestinal drugs. *Sucralfate* reduces absorption of levothyroxine from the gastrointestinal tract[1,2] as does *aluminium hydroxide*,[3] and *calcium carbonate*.[4,5]

1. Sherman SI, *et al.* Sucralfate causes malabsorption of L-thyroxine. *Am J Med* 1994; 96: 531–5.
2. Campbell JA, *et al.* Sucralfate and the absorption of L-thyroxine. *Ann Intern Med* 1994; 121: 152.
3. Liel Y, *et al.* Nonspecific intestinal adsorption of levothyroxine by aluminium hydroxide. *Am J Med* 1994; 97: 363–5.
4. Schneyer CR. Calcium carbonate and reduction of levothyroxine efficacy. *JAMA* 1998; 279: 750.
5. Singh N, *et al.* Effect of calcium carbonate on the absorption of levothyroxine. *JAMA* 2000; 283: 2822–5.

General anaesthetics. Severe hypertension and tachycardia have been reported[1] when *ketamine* was used in patients taking levothyroxine.

1. Kaplan JA, Cooperman LH. Alarming reactions to ketamine in patients taking thyroid medication-treatment with propranolol. *Anesthesiology* 1971; 35: 229–30.

Iron salts. *Ferrous sulfate* reduces absorption of levothyroxine from the gastrointestinal tract.[1]

1. Campbell NRC, *et al.* Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med* 1992; 117: 1010–13.

Lipid regulating drugs. Both decreased efficacy[1] and increased efficacy[2] of levothyroxine have been reported in individual patients given *lovastatin*. Increased thyroid stimulating hormone concentrations, requiring increased doses of levothyroxine, have been reported when *simvastatin* was begun.[3]

Colestyramine significantly reduces the absorption of levothyroxine by binding with thyroid hormones in the gastrointestinal tract. The malabsorption of levothyroxine is minimised by allowing an interval of 4 to 5 hours to elapse between taking the two drugs.[4] A similar effect has been seen with *colesevelam*, and a 4-hour interval is also recommended.[5,6]

1. Demke DM. Drug interaction between thyroxine and lovastatin. *N Engl J Med* 1989; 321: 1341–2.
2. Gormley GJ, Tobert JA. Drug interaction between thyroxine and lovastatin. *N Engl J Med* 1989; 321: 1342.
3. Kisch E, Segall HS. Interaction between simvastatin and L-thyroxine. *Ann Intern Med* 2005; 143: 547.
4. Northcutt RC, *et al.* The influence of cholestyramine on thyroxine absorpuon. *JAMA* 1969; 208: 1857–61.
5. Weitzman SP, *et al.* Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. *Thyroid* 2009; 19: 77–9.
6. Brown KS, *et al.* Effect of the bile acid sequestrant colesevelam on the pharmacokinetics of pioglitazone, repaglinide, estrogen estradiol, norethindrone, levothyroxine, and glyburide. *J Clin Pharmacol* 2010; 50: 554–65.

NSAIDs. Falsely low concentrations of levothyroxine (T_4) or tri-iodothyronine (T_3) have been reported during treatment with some anti-inflammatory drugs. Serum TSH measurements are less affected by NSAIDs and therefore TSH would be the optimal screening test in patients receiving an NSAID.[1]

1. Samuels MH, *et al.* Variable effects of nonsteroidal antiinflammatory agents on thyroid test results. *J Clin Endocrinol Metab* 2003; 88: 5710–16.

Orlistat. A case of symptomatic hypothyroidism within 2 weeks of commencing orlistat has been reported in a woman stabilised on thyroxine therapy.[1] US licensed product information recommends monitoring patients for changes in thyroid function if they are taking both levothyroxine and orlistat, and to administer the drugs at least 4 hours apart.

1. Madhava K, Hartley A. Hypothyroidism in thyroid carcinoma follow-up: orlistat may inhibit the absorption of thyroxine. *Clin Oncol (R Coll Radiol)* 2005; 17: 492.

Sex hormones. *Oestrogen* therapy increases serum concentrations of thyroxine-binding globulin, thus increasing the amount of bound thyroxine. Normal thyroid function stimulates thyroxine synthesis to compensate for this effect and maintain normal free-thyroxine serum concentrations. In hypothyroidism, however, patients treated with exogenous levothyroxine who receive oestrogens, as in oral contraceptives or HRT,[1] may require an increase in levothyroxine dose. In contrast, *androgens* reduce the concentration of the binding globulin, which has resulted in clinical hyperthyroidism when given to postmenopausal women maintained on levothyroxine replacement therapy.[2]

Increased levothyroxine requirements were noted in two women when they took *raloxifene* at the same time as levothyroxine; the effect could be reversed by separating doses of the two drugs by about 12 hours.[3,4]

1. Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *N Engl J Med* 2001; 344: 1743–9.
2. Arafah BM. Decreased levothyroxine requirement in women with hypothyroidism during androgen therapy for breast cancer. *Ann Intern Med* 1994; 121: 247–51.
3. Siraj ES, *et al.* Raloxifene causing malabsorption of levothyroxine. *Arch Intern Med* 2003; 163: 1367–70.
4. Garwood CL, *et al.* Increased thyroid-stimulating hormone levels associated with concomitant administration of levothyroxine and raloxifene. *Pharmacotherapy* 2006; 26: 881–5.

Sympathomimetics. Thyroid drugs increase metabolic demands and should therefore be used with caution with other drugs known to influence cardiac function, such as the *sympathomimetics*, as they may enhance this effect. In addition, thyroid hormones may increase receptor sensitivity to catecholamines.

Pharmacokinetics

Levothyroxine is variably absorbed from the gastrointestinal tract after oral doses. Fasting increases absorption. Once in the circulation, levothyroxine is extensively protein bound, mainly to thyroxine-binding globulin (TBG) but also to a lesser extent to thyroxine-binding pre-albumin (TBPA) or to albumin. Levothyroxine has a plasma half-life of about 6 to 7 days in euthyroid subjects; the half-life is prolonged in hypothyroidism and reduced in hyperthyroidism.

Levothyroxine is mainly metabolised in the liver and kidney to tri-iodothyronine (liothyronine) and, about 40%, to inactive reverse tri-iodothyronine (reverse T_3) both of which undergo further deiodination to inactive metabolites. Further metabolites result from conjugation and decarboxylation; tetra-iodothyroacetic acid (tetrac) is one such metabolite. Further hydrolysis of the conjugates releases free hormone, which can be reabsorbed in the intestine to undergo enterohepatic recycling. Some conjugates reach the colon unchanged, then undergo hydrolysis, and are eliminated in the faeces as free hormone. Levothyroxine is mainly eliminated by the kidneys as free drug, deiodinated metabolites, or conjugates.

The distribution of thyroid hormones into breast milk and across the placenta is discussed under Breast Feeding and Pregnancy (p. 2341.1 and p. 2341.2).

Absorption. A study found that patients with multinodular goitre and impaired acid secretion (such as *Helicobacter pylori*-related gastritis or atrophic gastritis) required increased doses of levothyroxine, suggesting that normal gastric acid secretion is necessary for effective absorption of oral levothyroxine.[1]

1. Centanni M, *et al.* Thyroxine in goiter, *Helicobacter pylori* infection, and chronic gastritis. *N Engl J Med* 2006; 354: 1787–95.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Euthyrox; Synthroid; T4; ***Austral.***: Eutroxsig; Oroxine; ***Austria***: Euthyrox; Thyrex; ***Belg.***: Elthyrone; Euthyrox; Thyrax; ***Braz.***: Euthyrox; Levoid; Puran T4; Synthroid; Tetroid; Tiroidin; ***Canad.***: Eltroxin; Euthyrox; Synthroid; ***Chile***: Esaldox; Eutirox; Synthroid; ***China***: Euthyrox (优甲乐); Letrox (雷替斯); Nei Zhang Qing (内隆清); You Xian (尤仙); Ze Ning (泽宁); ***Cz.***: Eltroxin; Euthyrox; Letrox; ***Denm.***: Eltroxin; Euthyrox; ***Fr.***: Levothyrox; ***Ger.***: Berlthyrox; Euthyrox; L-Thyrox†; Thevier; ***Gr.***: Euthyrox; Levothroid; Medithyrox; T4; Thyro-4; Thyrohormone; ***Hong Kong***: Eltroxin†; ***Hung.***: Euthyrox; Letrox; ***India***: Eltroxin; ***Indon.***: Euthyrox; Thyrax; ***Irl.***: Eltroxin; ***Israel***: Eltroxin; Euthyrox; ***Ital.***: Eutirox; Tiracrin; Tirosint; ***Jpn***: Thyradin-S; ***Malaysia***: Euthyrox; Oroxine; ***Mex.***: Abutiroi†; Cynocuatro; Eutirox; Karet; Leutiral; Tiroidine; ***Neth.***: Eltroxin; Euthyrox; Thyrax; Tirosint; ***Norw.***: Euthyrox; Levaxin; ***NZ***: Eltroxin; Eutroxsig; Synthroid; ***Philipp.***: Eltroxin; Eurolev; Euthyrox; Synthroid; Thyrax; Thyrohex†; ***Pol.***: Eferox†; Eltroxin; Euthyrox; Letrox; ***Port.***: Eutirox; Letequatro†; Letter; Thyrax; ***Rus.***: Bagothyrox (Баготирокс); Euthyrox (Эутирокс); ***S.Afr.***: Eltroxin; Euthyrox; Synthroid; ***Singapore***: Eltroxin; Euthyrox; Oroxine; Thyrosit; ***Spain***: Dexnon; Eutirox; Levothroid; ***Swed.***: Euthyrox; Levaxin; ***Switz.***: Eltroxine; Euthyrox; Tirosint; ***Thai.***: El-Thyro; Eltroxin; Euthyrox; Patroxin; Pondtroxin; Thyrosit; ***Turk.***: Euthyrox; Levotiron; Tefor; ***UK***: Eltroxin; Evotrox; ***Ukr.***: Euthirox (Эутирокс); Tivoral (Тиворал)†; ***USA***: Levothroid; Levoxyl; Novothyrox; Synthroid; Unithroid; ***Venez.***: Euthyrox; Thyrax.

Multi-ingredient Preparations. ***Arg.***: Eutroid; Levotrin; ***Austria***: Combithyrex; Jodthyrox; Novothyral; ***Belg.***: Novothyral; ***Chile***: Novothyral; ***Cz.***: Jodthyrox; Thyreotom; ***Fr.***: Euthyral; ***Ger.***: Jodthyrox; L-Thyrox Jod†; Novothyral; Prothyrid; Thyronajod; ***Gr.***: Dithyron; ***Ital.***: Dermocinetic; Somatoline; Tiroide Amsa; ***Mex.***: Cynoplus; Novotiral; ***Pol.***: Jodthyrox; Novothyral; ***Rus.***: Iodocomb (Йодокомб); Jodthyrox (Йодтирокс); Novothyral (Новотирал); Thyreocomb (Тиреокомб); Thyreotom (Тиреотом); ***S.Afr.***: Diotroxin; ***Switz.***: Novothyral; ***Turk.***: Bitiron†; ***USA***: Thyrolar.

Homoeopathic Preparations. ***Austria***: Lymphomyosot; Cz.: Lymphomyosot; ***Ger.***: Lymphomyosot N; Lymphomyosot; ***Hung.***: Lymphomyosot; ***S.Afr.***: Lymphomyosot; ***Ukr.***: Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Pharmacopoeial Preparations
BP 2014: Levothyroxine Oral Solution; Levothyroxine Tablets; **USP 36:** Levothyroxine Sodium Tablets; Liotrix Tablets.

Liothyronine Sodium *(BANM, rINNM)*

Liothyronin-Natrium; Liothyronin sodná sůl; Liothyronine sodique; Liothyroninum natricum; Liotironin Sodyum; Liotironina sódica; Liotironin-nátrium; Liotironino natrio druska; Liotyroniininatrium; Liotyronina sodowa; Liotyroninnatrium; Natrii Liothyroninum; Sodium Liothyronine; L-Triiodothyronine Sodium; Tri-iodotironin Sodyum; Натрий Лиотиронин; 3,5,3′-Tri-iodo-L-thyronine Sodium.

Sodium 4-*O*-(4-hydroxy-3-iodophenyl)-3,5-di-iodo-L-tyrosine.

$C_{15}H_{11}I_3NNaO_4$=673.0

CAS — 6893-02-3 (liothyronine); 55-06-1 (liothyronine sodium); 8065-29-0 (liotrix).

ATC — H03AA02.

ATC Vet — QH03AA02.

UNII — GCA9W7D2N.

NOTE. The abbreviation T_3 is often used for endogenous tri-iodothyronine in medical and biochemical reports. Liotrix is *USAN* for a mixture of liothyronine sodium with levothyroxine sodium.

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

Ph. Eur. 8: (Liothyronine Sodium). A white or slightly coloured, hygroscopic powder. Practically insoluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Liothyronine Sodium). A light tan, odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in most other organic solvents. Store in airtight containers.

Uses and Administration

Liothyronine is a thyroid hormone (see p. 2332.1). It is used in the treatment of hypothyroidism (p. 2333.3), and is believed to be more active than levothyroxine (p. 2339.2). The onset of action of liothyronine is rapid, developing within a few hours, and therefore it tends to be used in circumstances where this, and its short duration of action, are useful, particularly in hypothyroid (myxoedema) coma.

With regular dosing the peak therapeutic effect is usually achieved within 2 to 3 days; on withdrawal its effects may persist for 1 to 2 days.

The dose of liothyronine should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly. Although liothyronine is given as the sodium salt, doses can be expressed in terms of liothyronine sodium or liothyronine; the doses below are in terms of liothyronine sodium. Liothyronine sodium 10.3 micrograms is equivalent to about 10 micrograms of liothyronine. Liothyronine sodium 20 micrograms is generally considered to be equivalent in activity to about 100 micrograms of levothyroxine sodium.

In **hypothyroidism** the usual initial oral dose ranges from 5 to 25 micrograms daily, increased gradually to a maintenance dose of 60 to 75 micrograms daily in 2 or 3 divided doses, although up to 100 micrograms daily may be required in some patients. In elderly patients, in those with cardiovascular disorders, or in those with severe long-standing hypothyroidism, treatment should be introduced with doses at the low end of the range, with smaller increments, and longer intervals between increases, as necessary.

In **hypothyroid coma** liothyronine sodium may be given intravenously in a dose of 5 to 20 micrograms by slow intravenous injection, repeated as necessary, usually at intervals of 12 hours; the minimum interval between doses is 4 hours. An alternative regimen advocates an initial dose of 50 micrograms intravenously followed by further injections of 25 micrograms every 8 hours until improvement occurs; the dosage may then be reduced to 25 micrograms intravenously twice daily.

For the use of liothyronine in children, see below.

Liothyronine has also been given in the **diagnosis** of hyperthyroidism in adults. Failure to suppress the uptake of radio-iodine after several days of receiving liothyronine sodium suggests a diagnosis of hyperthyroidism.

For use as augmentation treatment with antidepressants, see Depression under Levothyroxine (p. 2340.1).

Liothyronine hydrochloride has also been used.

Administration in children. In the USA, liothyronine sodium may be given orally for the treatment of congenital hypothyroidism. An initial dose of 5 micrograms daily may be increased by 5 micrograms every 3 to 4 days, according to response, to the following usual maintenance doses:

- children below 1 year may require 20 micrograms daily
- children between 1 to 3 years may require 50 micrograms daily
- children over 3 years: as for adults, see p. 2342.3

In the UK, liothyronine sodium may be given orally to children for the treatment of hypothyroidism in a dose of 5 micrograms daily. However, the *BNFC* recommends that children aged 12 to 18 years can be given similar oral doses to those used in adults for hypothyroidism, namely 10 to 20 micrograms daily initially, increased gradually to 60 micrograms daily, in 2 or 3 divided doses. For the management of hypothyroid coma in children aged 12 to 18 years, intravenous doses are the same as for adults, see p. 2342.3.

Adverse Effects, Treatment, and Precautions

As for Levothyroxine Sodium, p. 2340.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies liothyronine 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)

Interactions

As for Levothyroxine Sodium, p. 2341.2.

Pharmacokinetics

Liothyronine is readily and almost completely absorbed from the gastrointestinal tract. Once in the circulation, liothyronine binds mainly to thyroxine-binding globulin (TBG), although less strongly than levothyroxine; some is also bound to thyroxine-binding pre-albumin (TBPA). Liothyronine has a plasma half-life in euthyroidism of about 1 to 2 days; the half-life is prolonged in hypothyroidism and reduced in hyperthyroidism.

Liothyronine is metabolised by deiodination to inactive di-iodothyronine and mono-iodothyronine. Iodine released by deiodination is largely reused within the thyroid cells. Further metabolites result from conjugation and decarboxylation; tiratricol (triac) is one such metabolite.

Thyroid hormones do not readily cross the placenta and minimal amounts are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Tertroxin; *Canad.*: Cytomel; *China*: Nei Zhang Qing (内障清); *Fr.*: Cynomel; *Ger.*: Thybon; Thyrotardin†; *Gr.*: Cynomel; T3; *Irl.*: Tertroxin†; *Ital.*: Liotir; Ti-Tre; *Mex.*: Cynomel; Liotrex†; Triyotex; *Neth.*: Cytomel; *NZ*: Tertroxin†; *Port.*: Neo-Tiroimade; *S.Afr.*: Tertroxin; *Turk.*: Tiromel; *UK*: Triiodothyronine Injection; *USA*: Cytomel; Triostat.

Multi-ingredient Preparations. *Arg.*: Eutroid; Levotrin; Tresite F; *Austria*: Combithyrex; Novothyral; *Belg.*: Novothyral; *Chile*: Novothyral; *Cz.*: Thyreotom; *Fr.*: Euthyral; *Ger.*: Novothyral; Prothyrid; *Gr.*: Dithyron; *Ital.*: Tiroide Amsa; *Mex.*: Cynoplus; Novotiral; Redotex; *Pol.*: Novothyral; *Rus.*: Novothyral (Новотирал); Thyreocomb (Тиреокомб); Thyreotom (Тиреотом); *S.Afr.*: Diotroxin; *Switz.*: Novothyral; *Turk.*: Bitiron†; *USA*: Thyrolar.

Homoeopathic Preparations. *Ger.*: NeyGeront Vitalkapsein A.

Pharmacopoeial Preparations
BP 2014: Liothyronine Tablets;
USP 36: Liothyronine Sodium Tablets; Liotrix Tablets.

Perchlorates

Перхлораты.

Potassium Perchlorate

Chloran Potasu; Chloristan draselný; Kalii Perchloras; Kālija Perhlorāts; Kalijev Perklorat; Kalio perchloratas; Kaliumperchloraat; Kaliumperchlorat; Kaliumperkloraatti; Kaliumperklorat; Kālium-perklorāt; Perclorato de Potássio; Perclorato di Potassio; Perclorato potásico; Potassium, perchlorate de; Potasyum Perklorat; Калиев Перхлорат; Перхлорат Калия.

$KClO_4$=138.5

CAS — 7778-74-7.

ATC — H03BC01.

ATC Vet — QH03BC01.

UNII — 42255P5X4D.

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

Ph. Eur. 8: (Potassium Perchlorate). A white or almost white crystalline powder or colourless crystals. Sparingly soluble in water; practically insoluble in alcohol.

USP 36: (Potassium Perchlorate). pH of a 0.1M solution in water is between 5.0 and 6.5.

Sodium Perchlorate

Chloristan Sodný; Natriumperchloraat; Natriumperchlorat; Natriumperkloraatti; Natriumperklorat; Perchlorate de Sodium; Perclorato de Sódio; Perclorato di Sodio; Perclorato sódico; Sodu nadchlorān; Перхлорат Натрия.

$NaClO_4$=122.4

CAS — 7601-89-0 (anhydrous sodium perchlorate); 7791-07-3 (sodium perchlorate monohydrate).

Uses and Administration

Potassium and sodium perchlorate reduce the uptake and concentration of iodide, pertechnetate, and other anions by the thyroid, choroid plexus, gastric mucosa, and salivary glands, probably by competitive inhibition of active transport mechanisms.

They have been used **diagnostically** as adjuncts to pertechnetate (^{99m}Tc) to enhance visualisation of the brain, Meckel's diverticulum, or the placenta by reducing unwanted images of other organs. The usual oral dose of either potassium or sodium perchlorate was 200 to 400 mg given 30 to 60 minutes before the use of sodium pertechnetate (^{99m}Tc).

Potassium and sodium perchlorate have also been used with sodium iodide (^{131}I) in the perchlorate discharge test of thyroid function. The release of radio-iodine from the gland after an oral dose of perchlorate indicates a defect in the binding of iodide by the thyroid and thus a defect in thyroid hormone synthesis. The test has also been used to investigate the action of antithyroid drugs.

Potassium and sodium perchlorate have been used in the treatment of **hyperthyroidism** (p. 2332.2), but because of toxicity have been largely replaced by alternative treatments. However, perchlorates may be useful in patients with iodine-induced hyperthyroidism such as that associated with amiodarone therapy, by increasing responsiveness to conventional antithyroid drugs. A typical oral dose of potassium perchlorate in amiodarone-induced hyperthyroidism is 1 g daily.

References.

1. Bartalena L, *et al.* Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. *J Clin Endocrinol Metab* 1996; 81: 2930–3.
2. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; 50: 89–105.
3. Soldin OP, *et al.* Perchlorate clinical pharmacology and human health: a review. *Ther Drug Monit* 2001; 23: 316–31.
4. Bartalena L, *et al.* Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin Endocrinol (Oxf)* 2004; 61: 494–502.
5. Bogazzi F, *et al.* Potassium perchlorate only temporarily restores euthyroidism in patients with amiodarone-induced hypothyroidism who continue amiodarone therapy. *J Endocrinol Invest* 2008; 31: 515–19.
6. Leung AM, *et al.* Perchlorate, iodine and the thyroid. *Best Pract Res Clin Endocrinol Metab* 2010; 24: 133–41.
7. Bogazzi F, *et al.* Approach to the patient with amiodarone-induced thyrotoxicosis. *J Clin Endocrinol Metab* 2010; 95: 2529–35.

Adverse Effects and Precautions

Potassium perchlorate seldom produces adverse effects when given as a single dose for diagnostic purposes. Prolonged use as an antithyroid drug has been associated with serious dose-related adverse effects. Aplastic anaemia (with some fatalities), agranulocytosis, eosinophilia, leucopenia, pancytopenia, and the nephrotic syndrome have been reported. Fever, rash, lymphadenopathy, gastrointestinal disturbances, arthralgia, and hypersensitivity reactions can occur. Hypothyroidism is common.

Effects on the blood. There have been reports of fatal aplastic anaemia[1,2] and of leucopenia and agranulocytosis[1] associated with the use of potassium perchlorate for the treatment of hyperthyroidism. A review[3] in 1998 noted that despite an increase in perchlorate use in recent years there did not appear to have been any further cases of aplastic anaemia since the 1960s.

1. Anonymous. Potassium perchlorate and aplastic anaemia. *BMJ* 1961; i: 1520–1.
2. Krevans JR, *et al.* Fatal aplastic anemia following use of potassium perchlorate in thyrotoxicosis. *JAMA* 1962; 181: 182–4.
3. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; 50: 89–105.

Handling. Potassium and sodium perchlorate have been used for the illicit preparation of explosives or fireworks; care is required with their supply. Great caution should be taken in handling perchlorates in solution or in the dry state as explosions may occur if brought into contact with organic or other readily oxidisable substances.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Irenat; *Canad.*: Perchloracap†; *Cz.*: Irenat; *Ger.*: Irenat; *Ital.*: Pertiroid; *Pol.*: Irenat†.

Pharmacopoeial Preparations
USP 36: Potassium Perchlorate Capsules.

Prolonium Iodide *(rINN)*

Ioduro de prolonio; Prolonii Iodidum; Prolonium, Iodure de; Yoduro de prolonio; Пролония Йодид.

NN-(2-Hydroxytrimethylene)bis(trimethylammonium) di-iodide.

$C_9H_{24}I_2N_2O$=430.1

CAS — 123-47-7.

UNII — VKH95UNQ6N.

Pharmacopoeias. In *Chin.*

Profile

Prolonium iodide has been given by injection as a source of iodine (p. 2336.3) as part of the treatment of thyroid storm and for the pre-operative management of hyperthyroidism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Luo Guan (洛冠).

Propylthiouracil *(BAN, rINN)*

Propiltiourasil; Propiltiouracil; Propiltiouracilas; Propiltiouracilo; Propylotiouracyl; Propylthiouracile; Propylthiouracilum; Propyltiouracil; Propyyltiourasiili; Пропилтиоурацил.

2,3-Dihydro-6-propyl-2-thioxopyrimidin-4(1*H*)-one; 2-Mercapto-6-propylpyrimidin-4-ol; 6-Propyl-2-thiouracil.

$C_7H_{10}N_2OS$=170.2

CAS — 51-52-5.

ATC — H03BA02.

ATC Vet — QH03BA02.

UNII — 721M9407IY.

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

Ph. Eur. 8: (Propylthiouracil). White or almost white crystals or crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 36: (Propylthiouracil). A white, powdery, crystalline substance. It is starch-like in appearance and to the touch. Slightly soluble in water, in chloroform, and in ether; sparingly soluble in alcohol; soluble in ammonium hydroxide and in alkali hydroxides. Protect from light.

Uses and Administration

Propylthiouracil is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p. 2332.1); it also inhibits the peripheral deiodination of thyroxine to tri-iodothyronine. It is used in the management of hyperthyroidism (p. 2344.1), including the treatment of Graves' disease, preparation of hyperthyroid patients for thyroidectomy, use as an adjunct to radio-iodine therapy, and the treatment of thyroid storm.

Propylthiouracil is usually given orally. Initial doses range from 200 to 400 mg daily, although in severe cases initial doses of 600 to 1200 mg daily have been used. It has often been given in divided daily doses but once daily dosage is also possible. Improvement is usually seen in 1 to 3 weeks and control of symptoms is achieved in 1 to 2 months. When the patient is euthyroid the dose is gradually

reduced to a maintenance dose, usually 50 to 150 mg daily. Treatment is usually continued for 1 to 2 years.

Doses should be reduced in renal impairment (below).

For the use of propylthiouracil in children and adolescents, see below.

Administration in children. In the UK, the *BNFC* recommends the following initial doses of oral propylthiouracil for children with hyperthyroidism (including Graves' disease), thyroid storm, and thyrotoxicosis:

- neonates: 2.5 to 5 mg/kg twice daily
- children aged 1 month to 1 year: 2.5 mg/kg three times daily
- children aged 1 to 5 years: 25 mg three times daily
- children aged 5 to 12 years: 50 mg three times daily
- children aged 12 to 18 years: 100 mg three times daily

These doses are given until the patient is euthyroid and then adjusted as needed; higher doses may be required, especially in thyroid storm.

In the USA, concerns about hepatotoxicity have prompted the FDA and others to advise against the routine use of propylthiouracil in children.[1,2]

1. FDA. Drug Safety Communication: new boxed warning on severe liver injury with propylthiouracil (issued 21st April, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm (accessed 29/06/10)
2. Rivkees SA, Mattison DR. Ending propylthiouracil-induced liver failure in children. *N Engl J Med* 2009; 360: 1574–5.

Administration in renal impairment. The oral dosage of propylthiouracil may need to be reduced in patients with renal impairment. The *BNF* suggests the following adjustment according to estimated glomerular filtration rate (eGFR):

- eGFR 10 to 50 mL/min per 1.73 m^2: doses should be reduced by 25%
- eGFR less than 10 mL/min per 1.73 m^2: reduce doses by 50%

Alcoholic liver disease. Propylthiouracil has been said to reduce hyperoxic liver injury in hypermetabolic *animals* and despite reports of hepatotoxicity, including some fatalities, associated with propylthiouracil (see Effects on the Liver, under Carbimazole, p. 2335.3), it has been investigated in the treatment of patients with alcoholic liver disease. A systematic review,[1] however, concluded that there is no evidence to substantiate this use. Propylthiouracil was associated with adverse effects and it could not be shown to have any significant effects on mortality, liver related mortality, liver complications, and liver histology.

1. Fede G, *et al.* Propylthiouracil for alcoholic liver disease. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2011 (accessed 02/08/11).

Hyperthyroidism. Propylthiouracil has been one of the mainstays in the treatment of hyperthyroidism (p. 2332.2). However, in 2010, the FDA highlighted the risk of severe liver injury associated with propylthiouracil.[1] It recommended that when starting treatment for hyperthyroidism, propylthiouracil should only be used in patients who cannot tolerate thiamazole, or when radioiodine therapy or surgery is not appropriate. It also recommended that propylthiouracil should not be used in children, except when other treatments are not appropriate. However, the FDA did consider that propylthiouracil may be the treatment of choice in the first trimester of pregnancy.

1. FDA. Drug Safety Communication: new boxed warning on severe liver injury with propylthiouracil (issued 21st April, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm (accessed 29/06/10)

Psoriasis. Several reports have described benefit in patients with psoriasis (p. 1688.1) given propylthiouracil. An oral dose of 300 mg daily for 8 to 12 weeks has been used and is said not to produce clinical hypothyroidism.[1]

1. Elias AN. Anti-thyroid thioureylenes in the treatment of psoriasis. *Med Hypotheses* 2004; 62: 431–7.

Adverse Effects, Treatment, and Precautions

As for Carbimazole, p. 2335.1, although cross-sensitivity to carbimazole does not necessarily occur.

Propylthiouracil has been associated with greater hepatotoxicity than other thiourea antithyroid drugs such as carbimazole or thiamazole (see Effects on the Liver, under Carbimazole, p. 2335.3). Patients or their carers should be told about this being a risk, especially in the first 6 months, how to recognise toxicity symptoms (e.g. anorexia, pruritus, jaundice, right upper quadrant pain), and that they should be advised to seek immediate medical attention. Doses may need to be reduced in hepatic impairment.

Propylthiouracil should be given with care, and in reduced doses, to patients with renal impairment.

Breast feeding. Propylthiouracil has been preferred to carbimazole or thiamazole since it enters breast milk less readily; for references, see Breast Feeding, under Carbimazole, p. 2335.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propylthiouracil 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 05/09/11)

Pharmacokinetics

Propylthiouracil is rapidly absorbed from the gastrointestinal tract with a 50 to 75% bioavailability and with peak plasma concentrations occurring about 1 to 2 hours after oral doses. It is concentrated in the thyroid gland; since its duration of action is more closely related to the intrathyroidal drug concentration than its plasma half-life, prolonged antithyroid activity results from single daily doses. Propylthiouracil is about 80% bound to plasma proteins.

Propylthiouracil has an elimination half-life of about 1 to 3 hours. It undergoes rapid first-pass metabolism in the liver, and is mainly excreted in the urine as the glucuronic acid conjugate, with very little excreted as unchanged drug. The elimination half-life may be increased in renal or hepatic impairment.

Propylthiouracil crosses the placenta and is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Prothiucil; ***Braz.***: Propil; Propiltacil; ***Canad.***: Propyl-Thyracil; ***China***: Ao Kang Xin (奥康欣); Bingsaiyou (丙赛优); Jiakang (甲康); ***Cz.***: Propycil; ***Fr.***: Propracyl; ***Ger.***: Propycil; ***Gr.***: Prothuril; ***Hong Kong***: CP-PTU; ***Hung.***: Propycil; ***Israel***: Propylthiocil; ***Pol.***: Thyrosan; ***Port.***: Propycil; ***Rus.***: Propycil (Пропицил); ***Singapore***: Propyl; ***Swed.***: Tiotil; ***Switz.***: Propycil; ***Thai.***: Peteyu; Propyl; PTU; Uracil; ***Turk.***: Propycil.

Pharmacopoeial Preparations

BP 2014: Propylthiouracil Tablets;

USP 36: Propylthiouracil Oral Suspension; Propylthiouracil Tablets.

Protirelin *(BAN, USAN, rINN)*

Abbott-38579; Lopremone; Protireliini; Protirelina; Protirelinas; Protiréline; Protirelinum; Synthetic TRH; Thyrotrophin-releasing Hormone; Thyrotropin-releasing Hormone; TRF; TRH; Протирелин.

L-Pyroglutamyl-L-histidyl-L-prolinamide; 1-[*N*-(5-Oxo-L-prolyl)-L-histidyl]-L-prolinamide; Glu-His-Pro-NH_2.

$C_{16}H_{22}N_6O_4$=362.4

CAS — 24305-27-9.

ATC — V04CJ02.

ATC Vet — QV04CJ02.

UNII — 5Y5F15120W.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*, which also includes the tartrate.

Ph. Eur. 8: (Protirelin). A synthetic tripeptide with the same sequence of amino acids as the natural hypothalamic neurohormone, that stimulates the release and synthesis of thyrotrophin. A white or yellowish-white hygroscopic powder. Very soluble in water; freely soluble in methyl alcohol. Store at a temperature of 2 degrees to 8 degrees. Protect from light and moisture.

Uses and Administration

Protirelin is a hypothalamic releasing hormone that stimulates the release of thyrotrophin (p. 2346.1) from the anterior lobe of the pituitary. It also has prolactin-releasing activity. It may be obtained by synthesis.

Protirelin may be used in the assessment of the hypothalamic-pituitary-thyroid axis in the diagnosis of mild hyperthyroidism (p. 2332.2) or hypothyroidism (p. 2333.3), and ophthalmic Graves' disease, although in many cases immunoassays for thyroid-stimulating hormone are now preferred. The response to protirelin may be used for differentiating between primary and secondary hypothyroidism but care is required in interpreting the results of the test and it should not be used alone in establishing the diagnosis. Protirelin is given with gonadorelin (p. 2280.3) in the assessment of anterior pituitary function.

Protirelin is given intravenously, usually in doses of 200 micrograms; doses up to 400 micrograms have been given. Protirelin is also given intranasally; 1 mg is sprayed into each nostril.

For the use of protirelin in children, see below.

Protirelin has been investigated in the treatment of neurological diseases, and in the prevention of neonatal respiratory distress syndrome, but results have been variable.

Protirelin tartrate has been given in the treatment of neurological disorders.

Administration in children. Protirelin is no longer available in the UK, but a single intravenous dose of 1 microgram/kg of protirelin was suggested for the assessment of thyroid function in children; the *BNFC* formerly recommended a single dose of 7 micrograms/kg (to a maximum of 200 micrograms), intravenously, for the diagnosis of hypopituitarism and hypothalamic disease.

Protirelin can also be given intranasally to children up to the age of 18 years; 1 mg is sprayed into one nostril only.

Lactation induction. Intranasal protirelin has been tried for stimulation of lactation (p. 2130.1) but good maternal education and support in techniques that promote physiological lactation are preferable to drug treatment.

Neonatal respiratory distress syndrome. The regulation of fetal lung development is under multihormonal control and thyroid hormones appear to stimulate pulmonary maturation. However, the thyroid hormones and thyrotrophin do not cross the placenta sufficiently for them to be given in premature labour where neonatal respiratory distress syndrome (p. 1608.3) may develop; therapy with protirelin has therefore been investigated.[1]

Protirelin has been given with corticosteroids to the mother and some beneficial effects have been noted.[1] One study using protirelin 400 micrograms every 8 hours for 4 doses indicated that antenatal protirelin reduced the incidence of chronic lung disease when given with corticosteroids but did not affect the incidence of respiratory distress syndrome.[2] However, 2 large multicentre studies had found that addition of protirelin to corticosteroid treatment had no beneficial effects on outcome compared with corticosteroids only;[3,4] in fact, in the earlier of these studies,[3] respiratory distress syndrome and the need for ventilation were greater in the offspring of mothers given protirelin. Subsequent follow-up appeared to confirm the disadvantages of protirelin in this cohort;[5] however the unexpected conclusions of this study aroused some controversy.[6-8] The second study noted no difference in outcome in the 2 groups of infants.[4] A meta-analysis concluded[9] that prenatal treatment with protirelin was not beneficial, and that it was associated with more adverse effects than the use of corticosteroids alone.

1. de Zegher F, *et al.* Prenatal treatment with thyrotrophin releasing hormone to prevent neonatal respiratory distress. *Arch Dis Child* 1992; 67: 450–4.
2. Ballard RA, *et al.* Respiratory disease in very-low-birthweight infants after prenatal thyrotropin-releasing hormone and glucocorticoid. *Lancet* 1992; 339: 510–5.
3. ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet* 1995; 345: 877–82.
4. Ballard RA, *et al.* Antenatal thyrotropin-releasing hormone to prevent lung disease in preterm infants. *N Engl J Med* 1998; 338: 493–8.
5. Crowther CA, *et al.* Australian collaborative trial of antenatal thyrotropin-releasing hormone: adverse effects at 12-month follow-up. *Pediatrics* 1997; 99: 311–17.
6. Ballard RA, *et al.* Thyrotropin-releasing hormone for prevention of neonatal respiratory disease. *Lancet* 1995; 345: 1572.
7. Moya FR, Maturana A. Thyrotropin-releasing hormone for prevention of neonatal respiratory disease. *Lancet* 1995; 345: 1572–3.
8. McCormick MC. The credibility of the ACTOBAT follow-up study. *Pediatrics* 1997; 99: 476–8.
9. Crowther CA, *et al.* Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 16/09/05).

Neurological disorders. Reports of the use of protirelin in various neurological disorders.

1. Bonuccelli U, *et al.* Oral thyrotropin-releasing hormone treatment in inherited ataxias. *Clin Neuropharmacol* 1988; 11: 520–8.
2. Filla A, *et al.* Sperimentazione cronica del TRH per via intramuscolare nelle degenerazioni spino-cerebellari: studio in doppio cieco cross-over su 30 soggetti. *Riv Neurol* 1989; 59: 83–8.
3. Mellow AM, *et al.* A peptide enhancement strategy in Alzheimer's disease: pilot study with TRH-physostigmine infusions. *Biol Psychiatry* 1993; 34: 271–3.
4. Chemaly R, *et al.* Myélinolyse extra-pontine: traitement par T.R.H. *Rev Neurol (Paris)* 1998; 154: 163–5.
5. Tzeng AC, *et al.* A study of thyrotropin-releasing hormone for the treatment of spinal muscular atrophy: a preliminary report. *Am J Phys Med Rehabil* 2000; 79: 435–40.
6. Kubek MJ, Garg BP. Thyrotropin-releasing hormone in the treatment of intractable epilepsy. *Pediatr Neurol* 2002; 26: 9–17.

Adverse Effects

Protirelin given by rapid intravenous injection may cause nausea, a desire to micturate, flushing, dizziness, and a strange taste. These effects have been attributed to contraction of smooth muscles by the bolus injection. Similar adverse effects have been seen with intranasal application; bronchospasm can also occur. Transient increases in pulse rate, and changes in blood pressure have been reported with intravenous use. Convulsions have occurred in patients with predisposing conditions such as

epilepsy, brain lesions, or pituitary tumours. In patients with pituitary tumours given protirelin with gonadorelin, severe headaches with or without amaurosis have been reported, as has pituitary apoplexy requiring neurosurgical intervention.

Amaurosis. Of 4 patients with pituitary tumours who developed severe headache after protirelin injection, one also developed amaurosis, apparently associated with pituitary apoplexy.[1] Visual acuity improved after surgery.

1. Drury PL, *et al.* Transient amaurosis and headache after thyrotropin releasing hormone. *Lancet* 1982; I: 218–19.

Effects on the cardiovascular system. Increased blood pressure has been reported in women given protirelin antenatally,[1,2] and the view has been expressed that although the magnitude of the change is unlikely to be clinically significant in normotensive women, much greater rises have been seen in pre-eclamptic women[2,3] and may be severe enough to increase the risk of cerebral haemorrhage.[2]

1. ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet* 1995; 345: 877–82.
2. Peek MJ, *et al.* Hypertensive effect of antenatal thyrotropin-releasing hormone in pre-eclampsia. *Lancet* 1995; 345: 793. Correction. *ibid.*: 1124.
3. Tan ASA, *et al.* Is maternal thyrotropin releasing hormone administration safe in the pregnant women with preeclampsia? *Am J Perinatol* 1997; 14: 5–6.

Effects on the CNS. Adverse effects reported after injection of 400 micrograms of protirelin included unconsciousness, hypotension, and convulsions.[1] In another patient with a history of convulsions, a 500-microgram injection induced epileptic seizures.[2]

1. Dolva LØ, *et al.* Side effects of thyrotrophin releasing hormone. *BMJ* 1983; 287: 532.
2. Maeda K, Tanimoto K. Epileptic seizures induced by thyrotropin releasing hormone. *Lancet* 1981; i: 1058–9.

Effects on the respiratory system. Bronchospasm occurred in an asthmatic boy given protirelin intravenously.[1]

For a report that protirelin provoked bronchospasm in patients with motor neurone disease, see under Precautions, below.

1. McFadden RG, *et al.* TRH and bronchospasm. *Lancet* 1981; ii: 758–9.

Effect on sexual function. On questioning, 7 of 16 women reported a sensation of mild vaginal sexual arousal occurring 1 to 3 minutes after intravenous injection of protirelin.[1] Four women also had urinary sensations, and 3 described an urge to urinate with no sexual component.

1. Blum M, Pulini M. Vaginal sensations after injection of thyrotropin releasing hormone. *Lancet* 1980; ii: 43.

Pituitary apoplexy. Pituitary apoplexy has been reported after combined testing of anterior pituitary function in patients with a pituitary tumour.[1,2] Of the drugs given, protirelin was thought most likely to have an aetiological role. Pituitary apoplexy has also been reported after the use of protirelin alone.[3]

See also Amaurosis, above.

1. Chapman AJ, *et al.* Pituitary apoplexy after combined test of anterior pituitary function. *BMJ* 1985; 291: 26.
2. Dökmetaş HS, *et al.* Pituitary apoplexy probably due to TRH and GnRH stimulation tests in a patient with acromegaly. *J Endocrinol Invest* 1999; 22: 698–700.
3. Szabolcs I, *et al.* Apoplexy of a pituitary macroadenoma as a severe complication of preoperative thyrotropin-releasing hormone (TRH) testing. *Exp Clin Endocrinol Diabetes* 1997; 105: 234–6.

Precautions

Protirelin should be given with care to patients with ischaemic heart disease, obstructive airways disease, epilepsy, pituitary tumours, or severe hypopituitarism. Giving protirelin while the patient is lying down may reduce the incidence of hypotension.

Eclampsia. For the suggestion that the hypertensive effects of protirelin increase the risk of cerebral haemorrhage in pre-eclamptic women, see Effects on the Cardiovascular System under Adverse Effects, above.

Motor neurone disease. In some patients with amyotrophic lateral sclerosis, intravenous injection of protirelin resulted in acute bronchospasm.[1] Five of 25 patients had falls in FEV_1 of more than 20%; in 2, a 15% decrease in arterial-oxygen pressure occurred. Patients with sclerosis and weakened respiratory muscles should be warned of this potential adverse effect.

1. Braun SR, *et al.* Pulmonary effects of thyrotropin-releasing hormone in amyotrophic lateral sclerosis. *Lancet* 1984; ii: 529–30.

Interactions

The thyroid-stimulating hormone (TSH) response to protirelin may be *decreased* by the thyroid hormones levothyroxine and liothyronine, barbiturates, bromocriptine, carbamazepine, corticosteroids (at pharmacological rather than physiological doses), cyproheptadine, dopamine, levodopa, lisuride, methysergide, morphine, phenothiazines (such as thioridazine), phentolamine, salicylates (such as aspirin), somatostatin, ranitidine, and X-ray contrast media.

An *increased* response may be seen with antithyroid drugs (if the patient is over-treated), gonadorelin and gonadorelin analogues, amiodarone, biperiden, clomifene, domperidone, haloperidol, iodides, metoclopramide, prostaglandins, spironolactone, and sulpiride. Since caffeine and theophylline also enhance the response, tea and coffee or other xanthine-containing beverages should be avoided for 12 to 14 hours before use of protirelin.

Oestrogens may also increase the response in men but not usually in women; when combined with a progestogen a slightly depressed response has been reported.

Variable responses have been seen with chlorpromazine and lithium.

Reviews.

1. Lamberg B-A, Gordin A. Abnormalities of thyrotrophin secretion and clinical implications of the thyrotrophin releasing hormone stimulation test. *Ann Clin Res* 1978; 10: 171–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: TRH; Trhelea; *Austria*: Antepan; *Canad.*: Relefact TRH†; *Fr.*: Stimu-TSH†; *Ger.*: Antepan†; Thyroliberin†; TRH; *Gr.*: Relefact†; TRH; *Israel*: TRH; *Jpn*: Hirtonin; *Neth.*: Relefact TRH; *Singapore*: TRH; *Spain*: TRH Prem†; *Turk.*: TRH.

Thiamazole *(BAN, rINN)*

Mercazolylum; Methimazole; Methylmercaptoimidazole; Metimazol; Thiamazol; Thiamazolum; Tiamatsoli; Tiamazol; Tiamazolas; Тиамазол.

1-Methylimidazole-2-thiol.

$C_4H_6N_2S$=114.2

CAS — 60-56-0.

ATC — H03BB02.

ATC Vet — QH03BB02.

UNII — 554Z48XN5E.

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

Ph. Eur. 8: (Thiamazole). A white or pale brown, crystalline powder. Freely soluble in water and in dichloromethane; freely soluble or soluble in alcohol.

USP 36: (Methimazole). A white to pale buff crystalline powder having a faint characteristic odour. Soluble 1 in 5 of water, 1 in 5 of alcohol, 1 in 4.5 of chloroform, and 1 in 125 of ether. Its solutions are practically neutral to litmus. Protect from light.

Uses and Administration

Thiamazole is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p. 2332.1). It is used in the management of hyperthyroidism (p. 2332.2), including the treatment of Graves' disease, in the preparation of hyperthyroid patients for thyroidectomy, as an adjunct to radio-iodine therapy, and in the treatment of thyroid storm.

Thiamazole is given orally usually in an initial dosage of 15 to 60 mg daily. It is usually given in three divided doses but single daily doses have also been used. When the patient is euthyroid the dose is gradually reduced to a maintenance dose, usually 5 to 15 mg daily. Maintenance treatment is usually continued for 1 to 2 years, although the optimum duration has not been established.

Thiamazole has also been used with supplemental levothyroxine as a *blocking-replacement regimen*.

Thiamazole doses of 80 to 240 mg daily, usually in 3 or 4 divided doses, have been given intravenously in the management of thyroid storm.

For the use of thiamazole in children, see below.

Administration in children. The initial oral dose of thiamazole for hyperthyroidism in children is 400 micrograms/kg daily, in 3 divided doses; the maintenance dose may be half of this.

Adverse Effects, Treatment, and Precautions

As for Carbimazole, p. 2335.1.

Breast feeding. The use of thiamazole during breast feeding is discussed under Carbimazole, p. 2335.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thiamazole 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 05/09/11)

Pharmacokinetics

The pharmacokinetics of thiamazole can be considered with those of carbimazole (p. 2336.2) since the latter is rapidly and completely metabolised to thiamazole in the body.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Danantizol; *Belg.*: Strumazol; *Braz.*: Tapazol; *Canad.*: Tapazole; *Chile*: Thyrozol; *China*: Jia Qi Ya (佳琪亚); Thyrozol (赛治); *Cz.*: Thyrozol; *Denm.*: Thycapzol; *Fr.*: Thyrozol; *Ger.*: Favistan; Methizol; Thyrozol; *Gr.*: Unimazole; *Hung.*: Metothyrin; *India*: Methimez; *Indon.*: Thyrozol; *Israel*: Mercaptizol; *Ital.*: Tapazole; *Malaysia*: Timazol; *Mex.*: Ganglioside; Tapazol; Tizorol; *Neth.*: Strumazol; *Philipp.*: Strumazol; Tapazole; Tapdin; Thyrazol; *Pol.*: Metizol; Thyrozol; *Port.*: Metibasol; *Rus.*: Mercazolil (Мерказолил); Thyrozol (Тирозол); *Singapore*: Thyrozol; *Spain*: Tirodril; *Swed.*: Thacapzol; *Thai.*: Tapazole; Timazol; *Turk.*: Thyromazol; *Ukr.*: Metizol (Метизол); Thyrozol (Тирозол); *USA*: Northyx; Tapazole; *Venez.*: Tapazol.

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

Pharmacopoeial Preparations

USP 36: Methimazole Tablets.

Thyroglobulin *(USAN, rINN)*

Thyreoglobulin; Thyreoglobuline; Thyroglobuline; Thyroglobulinum; Tireoglobulin; Tireoglobulina; Tiroglobulina; Tyreoglobullini; Tyreoglobulina; Тиреоглобулин.

CAS — 9010-34-8.

UNII — NN2P9VPL7M.

Profile

Thyroglobulin is an extract obtained by the fractionation of porcine thyroid glands, that yields levothyroxine and liothyronine on hydrolysis. It has been used in the treatment of hypothyroidism, but such treatment with mixtures of thyroid hormones or preparations of animal extracts is not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Tiroide Vister.

Thyroid

Dry Thyroid; Getrocknete Schilddrüse; Glandă Tiroidă; Glandula Thyreoidea; Glándula tiroides, extracto de; Kilpirauhanen; NSC-26492; Pajzsmirigy; Schildklier; Ščitnica; Skildklier; Skjaldkirtill; Skjoldbruskkirtel; Skjoldbruskkjertel; Sköldkörtel; Skydliaukė; Štítná Žláza; Štitna Žlijezda; Štítna Žľaza; Tarczyca; Theiroid; Thyreoidin; Thyroid Extract; Thyroid Gland; Thyroïde; Thyroidea; Thyroideum Siccum; Tiroide; Tiroide Secca; Tiroit Bezi; Vairogdziedzeris; Щитовидна Жлеза; Щитовидная Железа.

ATC — H03AA05.

ATC Vet — QH03AA05.

UNII — 0B4FDL9I6P.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Thyroid). It is the cleaned, dried, and powdered thyroid gland, previously deprived of connective tissue and fat, obtained from domesticated animals used for food by humans. On hydrolysis it yields not less than 90% and not more than 110% each of the labelled amounts of levothyroxine and liothyronine calculated on the dried basis. It is free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. It may contain a suitable diluent such as glucose, lactose, sodium chloride, starch, or sucrose. A yellowish to buff-coloured amorphous powder, having a slight, characteristic, meat-like odour. Store in airtight containers.

Profile

Thyroid has been used in the treatment of hypothyroidism, but treatment with mixtures of thyroid hormones or preparations of animal extracts is not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Cinetic; *Mex.*: Amet†; *Thai.*: Thiroyd; Thyroid-S; TR; *USA*: Nature Throid; Westhroid.

Multi-ingredient Preparations. *Ger.*: FegaCoren; *India*: Ebexid; *Thai.*: Metharmon-Ft.

Homoeopathic Preparations. *Canad.*: Fucus L111†; Weight Control; *Chile*: Fucus Especial; *Fr.*: Fucus Complexe No 111; *Ger.*: AntiFocal Nr 69-Sol L†; Glandulae-F-Gastreu R20; Hewethyreon N; NeyDil Nr 66†; NeyFoc Nr 69; NeyLing Nr 66; NeySol L 66†; *Neth.*: Chavita 5.

Pharmacopoeial Preparations
USP 36: Thyroid Tablets.

Thyrotrophin *(BAN, rINN)*

Hormona tirotrófica; Thyroid-stimulating Hormone; Thyrotrophic Hormone; Thyrotrophine; Thyrotrophinum; Thyrotropin; Thyrotropinum; Tirotrofina; TSH; Tyrotropiini; Tyrotropin; Тиротропин.

CAS — 9002-71-5.
ATC — H01AB01; V04CJ01.
ATC Vet — QH01AB01; QV04CJ01.
UNII — 02K5I6Z9AK.

Description. Thyrotrophin is a glycoprotein from the anterior pituitary with a molecular weight in man of about 30 000.

Thyrotropin Alfa *(BAN, USAN, rINN)*

rhTSH; Thyrotropine Alfa; Thyrotropinum Alfa; Tirotropina alfa; Тиротропин Альфа.

CAS — 194100-83-9.
ATC — V04CJ01.
ATC Vet — QV04CJ01.
UNII — AVX3D5A4LM.

Units

0.037 units of human pituitary thyrotrophin for immunoassay and bioassay are contained in about 7.5 micrograms of thyrotrophin, with albumin 1 mg and lactose 5 mg, in one ampoule of the second International Reference Preparation (1983).

Uses and Administration

Thyrotrophin is a glycoprotein that is secreted by the anterior lobe of the pituitary and has an alpha subunit essentially the same as that of the gonadotrophins. Its main actions are to increase iodine uptake by the thyroid and the formation and secretion of the thyroid hormones. It may produce hyperplasia of thyroid tissue. Thyrotrophin secretion is controlled by a hypothalamic releasing hormone (Protirelin, p. 2344.2) and by circulating thyroid hormones; somatostatin (p. 1930.3) inhibits the release of thyrotrophin.

Thyrotrophin was used with radio-iodine in the diagnosis of hypothyroidism (p. 2333.3) and to differentiate between primary and secondary hypothyroidism, but direct radioimmunoassay of circulating endogenous thyroid-stimulating hormone has superseded this test.

Thyrotropin alfa is a recombinant form of thyrotrophin used as an adjunctive diagnostic tool for serum-thyroglobulin testing, with or without radio-iodine imaging, in the follow-up of patients with well-differentiated thyroid cancer. It is also used to increase radio-iodine uptake for ablation of thyroid remnant tissue in patients who have had a thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic disease. The usual thyrotropin alfa regimen consists of 2 doses of 900 micrograms, given 24 hours apart, by intramuscular injection into the buttock. Radio-iodine is given 24 hours after the second dose of thyrotropin alfa for radio-iodine imaging or remnant ablation. Diagnostic scanning is performed 48 to 72 hours after the radio-iodine has been given, but post-therapy scanning may be delayed by additional days to allow background activity to decline. Samples for serum-thyroglobulin testing should be taken 72 hours after the second thyrotropin alfa dose.

Goitre and thyroid nodules. Thyrotropin alfa has been investigated[1-4] as an adjunct to increase thyroid uptake of radio-iodine (^{131}I) in the treatment of selected patients with nodular goitre (p. 2332.1).

1. Nielsen VE, *et al.* The effects of recombinant human thyrotropin, in normal subjects and patients with goitre. *Clin Endocrinol (Oxf)* 2004; 61: 655–63.
2. Duick DS, Baskin HJ. Significance of radioiodine uptake at 72 hours versus 24 hours after pretreatment with recombinant human thyrotropin for enhancement of radioiodine therapy in patients with symptomatic nontoxic or toxic multinodular goiter. *Endocr Pract* 2004; 10: 253–60.
3. Nielsen VE, *et al.* Recombinant human thyrotropin markedly changes the ^{131}I kinetics during ^{131}I therapy of patients with nodular goiter: an evaluation by a randomized double-blinded trial. *J Clin Endocrinol Metab* 2005; 90: 79–83.
4. Albino CC, *et al.* Recombinant human thyrotropin as adjuvant in the treatment of multinodular goiters with radioiodine. *J Clin Endocrinol Metab* 2005; 90: 2775–80.

Malignant neoplasms of the thyroid. Patients with well-differentiated thyroid carcinoma (p. 716.1) undergo surgery, with or without iodine-131 treatment. They then receive thyroid hormone therapy to suppress thyrotrophin (TSH), because most differentiated thyroid cancers express TSH receptors and grow in response to thyrotrophin stimulation. Monitoring for tumour recurrence in subsequent years requires interruption of thyroid hormone treatment so that thyrotrophin levels rise, and stimulate the uptake of a subsequent dose of iodine-131 by any residual or recurrent tumour. However, this results in hypothyroidism, with associated symptoms that may be severe in some patients.[1]

Studies[2,3] have examined the use of thyrotropin alfa as an alternative prelude to radio-iodine scanning, and found that it did stimulate radio-iodine uptake, although the sensitivity of scanning may depend on the technique used; thyrotropin alfa might be considered a suitable alternative to thyroid hormone withdrawal. In patients with CNS or spinal metastases, or who have substantial disease in the thyroid bed, thyrotropin alfa may cause tumour expansion with acute complications; it has been recommended[1] that prophylactic corticosteroid therapy should be considered in these cases.

Thyroid hormone withdrawal is also used in the treatment of differentiated thyroid cancer, to increase uptake of radio-iodine for thyroid remnant ablation and treatment of metastatic disease. Thyrotropin alfa is also used as an alternative adjunct.[4]

1. Basaria M, *et al.* The use of recombinant thyrotropin in the follow-up of patients with differentiated thyroid cancer. *Am J Med* 2002; 112: 721–5.
2. Ladenson PW, *et al.* Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. *N Engl J Med* 1997; 337: 888–96.
3. Haugen BR, *et al.* A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab* 1999; 84: 3877–85.
4. Robbins RJ, Robbins AK. Recombinant human thyrotropin and thyroid cancer management. *J Clin Endocrinol Metab* 2003; 88: 1993–8.

Adverse Effects, Treatment, and Precautions

The most common adverse effects with thyrotropin alfa are nausea and headache. Vomiting, diarrhoea, dizziness, paraesthesia, fatigue, and insomnia are also common. Hypersensitivity reactions have been reported rarely; manifestations include urticaria, rash, pruritus, flushing, and respiratory signs and symptoms. A transient flu-like illness has also been reported, which may include fever, chills, myalgia, and arthralgia. Other adverse effects include nasopharyngitis, tremors, palpitations, hyperhidrosis, and discomfort at the injection site.

Very rare cases of hyperthyroidism or atrial fibrillation have been seen when thyrotropin alfa has been given to patients with residual thyroid tissue. Fatalities due to drug-induced hyperthyroidism have been reported within 24 hours of use of thyrotropin alfa; these occurred in patients with multiple serious comorbidities, and caution is recommended in patients with cardiac disease, extensive metastases, or serious underlying illness. Enlargement of residual thyroid tissue or metastases can occur after treatment, which may cause pain and acute symptoms dependent on the location of the tissue; for example, hemiplegia, hemiparesis, or loss of vision have occurred in patients with CNS metastases. Laryngeal oedema with respiratory distress, necessitating tracheotomy, has been reported in patients with paratracheal metastases. Pretreatment with corticosteroids is recommended for patients in whom tumour enlargement might compromise vital anatomical structures.

The elimination of thyrotropin alfa is reduced in dialysis-dependent end-stage renal disease, resulting in prolonged elevation of thyroid-stimulating hormone concentrations after treatment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thyrotropin as not porphyrinogenic when used as a diagnostic agent; 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)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Thyrogen; *Belg.*: Thyrogen; *Canad.*: Thyrogen; *Chile*: Thyrogen; Cz.: Thyrogen; *Denm.*: Thyrogen; *Fin.*: Thyrogen; *Fr.*: Thyrogen; *Ger.*: Thyrogen; *Gr.*: Thyrogen; *Hong Kong*: Thyrogen; *Hung.*: Thyrogen; *Irl.*: Thyrogen; *Israel*: Thyrogen; *Ital.*: Thyrogen; *Jpn*: Thyrogen; *Malaysia*: Thyrogen; *Neth.*: Thyrogen; *Norw.*: Thyrogen; *Pol.*: Thyrogen; *Port.*: Thyrogen; *Singapore*: Thyrogen; *Spain*: Thyrogen; *Swed.*: Thyrogen; *Switz.*: Thyrogen; *Thai.*: Thyrogen; *Turk.*: Thyrogen; *UK*: Thyrogen; *Ukr.*: Tirogen (Тироген); *USA*: Thyrogen.

Tiratricol *(rINN)*

Tiratricolum; Tiratrikol; Tiratrikoli; Triac; Triiodothyroacetic Acid; Тиратрикол.

[4-(4-Hydroxy-3-iodophenoxy)-3,5-di-iodophenyl]acetic acid.

$C_{14}H_9I_3O_4$=621.9
CAS — 51-24-1.
ATC — D11AX08; H03AA04.
ATC Vet — QD11AX08; QH03AA04.
UNII — 29OQ9EU4R1.

NOTE. Tri-ac has also been used as a name for proprietary preparations containing other drugs.

Profile

Tiratricol, a metabolite of tri-iodothyronine, is given orally to suppress the secretion of thyroid-stimulating hormone (TSH). It is given with thyroxine in situations where thyroxine monotherapy is insufficient to suppress TSH secretion. It is reported to be less active than the thyroid hormones.

Obesity. Abnormal thyroid function tests, severe diarrhoea, fatigue, lethargy, and profound weight loss have occurred in patients taking dietary supplements containing tiratricol.[1-3] The FDA has warned that dietary supplements containing tiratricol may cause heart attacks and strokes.[4]

1. Anonymous. Triax: a harmful product sold on the internet. *WHO Drug Inf* 2000; 14: 30.
2. Bauer BA, *et al.* Symptomatic hyperthyroidism in a patient taking the dietary supplement tiratricol. *Mayo Clin Proc* 2002; 77: 587–90.
3. Ma RC, *et al.* Thyroid dysfunction due to over-the-counter usage of tiratricol. *Intern Med J* 2008; 38: 611–12.
4. FDA. Safety alert for human medical products: tiratricol (triiodothyroacetic acid) (issued 22nd November 2000). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm173259.htm (accessed 18/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nulobes; Triacana; *Fr.*: Teatrois.

Urological Drugs

Benign prostatic hyperplasia, p. 2347
Cystitis, p. 2347
Haemorrhagic cystitis, p. 2347
Interstitial cystitis, p. 2348
Diabetes insipidus, p. 2348
Erectile dysfunction, p. 2348
Glomerular kidney disease, p. 2349
Malignant neoplasms, p. 2349
Micturition disorders, p. 2349
Nocturnal enuresis, p. 2349
Urinary incontinence and retention, p. 2349
Premature ejaculation, p. 2350
Prostatitis, p. 2350
Renal calculi, p. 2350
Renal colic, p. 2351
Renal failure, p. 2351
Sexually transmitted diseases, p. 2351
Syndrome of inappropriate ADH secretion, p. 2351
Urinary-tract infections, p. 2351

This chapter includes a number of drugs used in the management of certain urological or urogenital conditions such as urinary incontinence, benign prostatic hyperplasia, and erectile dysfunction.

Other drugs used in these conditions may be found elsewhere in *Martindale*: they include the tricyclic antidepressants such as imipramine (p. 426.2) and the serotonin and noradrenaline reuptake inhibitor duloxetine (p. 415.1), which are in the chapter on Antidepressants (p. 397.1); some alpha blockers such as doxazosin (p. 1369.1), phentolamine (p. 1468.3), and prazosin (p. 1473.3), as well as, more generally, diuretics and drugs such as ACE inhibitors which may be used to alter urological function, all of which are to be found in the chapter on Cardiovascular Drugs (p. 1242.1); and the various electrolytes (see p. 1775.1).

For the treatment of urogenital infections, see under Choice of Antibacterial, p. 172.2. For the management of urological and reproductive tract malignancies, see under Choice of Antineoplastic, p. 691.2.

Benign prostatic hyperplasia

Benign enlargement of the prostate gland is common in men with increasing age: at least 50% of men aged over 60 years have histological evidence of hyperplasia. Men with an enlarged prostate may have symptoms of lower urinary tract obstruction (often referred to as LUTS), such as acute or chronic urinary retention, or irritative symptoms such as frequency, urgency, nocturia, or occasionally urge incontinence, resulting from secondary bladder instability. Therapy is influenced by the severity of symptoms and their effect on the patient's quality of life. The three main options for management are watchful waiting (monitoring without active intervention), drug treatment, and surgery.[1-7]

Watchful waiting is suitable for men with mild to moderate symptoms that are not bothersome,[2,3] and for some men with moderate to severe LUTS who have not yet developed complications of benign prostatic hyperplasia such as renal impairment, urinary retention, or recurrent infection.[2] The patient is monitored and advised on lifestyle measures that may improve symptoms; these include decreasing fluid intake at specific times such as bedtime or when going out, reducing caffeine and alcohol intake in general, and bladder re-training techniques.

Drug treatment is essentially based on the use of *alpha$_1$-adrenoceptor blockers* and *5α-reductase inhibitors*, and is begun once symptoms become bothersome.

- Alpha$_1$-adrenoceptor blockers (such as alfuzosin, doxazosin, prazosin, indoramin, tamsulosin, or terazosin) apparently act on the smooth muscle tone within the prostate and the bladder neck, and can produce symptomatic relief within weeks.[1-3] They are considered to have similar efficacy[1-3,8] and choice between them may be influenced by adverse effect profile and ease of use.[8]
- The 5α-reductase inhibitors (finasteride and dutasteride) reduce prostate volume, although this takes a number of months.[1,3,8] They reduce the risk of progression to urinary retention and prostatic surgery, and are given particularly to men with urinary symptoms and large prostates.[1-3,8] However, they are less effective for symptomatic improvement than alpha$_1$-adrenoceptor blockers.[2]
- Combined treatment using an alpha$_1$-adrenoceptor blocker and a 5α-reductase inhibitor may be more effective than monotherapy,[1,3] and is considered to be suitable for patients with LUTS associated with demonstrable prostatic enlargement who are at significant risk of progression.[2,3,8]

More recently there has been interest in the use of *phosphodiesterase type-5 inhibitors* such as tadalafil, which cause smooth-muscle relaxation in the bladder neck, urethra, and prostate.[9]

Other drug therapies exist but are largely unproven or unsuitable for general use. Gonadorelin analogues such as leuprorelin or nafarelin can produce a reduction in prostate size, but adverse effects make these drugs unsuitable for indefinite therapy. More recently, gonadorelin antagonists such as cetrorelix have been tried. The antifungal mepartricin has been reported to produce symptomatic improvement, possibly by binding to oestrogen in the intestinal lumen and lowering plasma-oestrogen concentrations. Injection of botulinum A toxin into the prostate gland, for the treatment of chronic urinary retention, has shown some promise in small studies. A number of plant extracts such as saw palmetto (*Serenoa repens*) and *Pygeum africanum* are also in use. Systematic reviews of the latter[10] and of the phytosterol sitosterol[11] (a constituent of both plants) in benign prostatic hyperplasia have noted some benefits; however, most studies were short-term and used preparations that were not standardised, and a subsequent review of saw palmetto[12] found little evidence of efficacy. Although there have been concerns about the use of antimuscarinics in patients with symptomatic disease, some patients have symptoms suggestive of overactive bladder, and antimuscarinics such as oxybutynin may be useful to decrease hypercontractility of the detrusor muscle and reduce overactive bladder symptoms, either alone or as adjuncts (see also Urinary Incontinence and Retention, p. 2349.2).[2,3,6]

Surgery is recommended for men with more severe symptoms that do not respond to drug therapy, or who have complications such as acute urinary retention, gross haematuria, renal failure, bladder calculi, or recurrent urinary-tract infection. The mainstay of treatment is transurethral resection of the prostate (TURP),[1,2] which is more effective than drug treatment but is associated with a risk of complications such as impotence (although this may not be attributable to the surgery in all cases) and bladder neck contracture.[2] Transurethral incision of the prostate may be used as an alternative for smaller prostates[1,2] and open prostatectomy may be indicated for removal of very large glands. Various surgical alternatives to TURP use heat to destroy prostatic tissue surrounding the urethra.[1,2,13] These minimally invasive therapies include transurethral microwave thermotherapy, water-induced thermotherapy, radiofrequency transurethral needle ablation, interstitial laser treatment, and transrectal high-intensity focused ultrasound.

1. Thorpe A, Neal D. Benign prostatic hyperplasia. *Lancet* 2003; 361: 1359–67. Correction. *ibid.*: 362: 496.
2. McVary KT, *et al.* American Urological Association. American Urological Association guideline: management of benign prostatic hyperplasia (BPH) (revised 2010). Available at: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=bph (accessed 18/04/11)
3. Oelke M, *et al.* European Association of Urology. Guidelines on conservative treatment of non-neurogenic male LUTS (2010). Available at: http://www.uroweb.org/gls/pdf/BPH%202010.pdf (accessed 18/04/11)
4. McNaughton-Collins M, Barry MJ. Managing patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Am J Med* 2005; 118: 1331–9.
5. Patel AK, Chapple CR. Benign prostatic hyperplasia: treatment in primary care. *BMJ* 2006; 333: 535–9.
6. Wilt TJ, N'Dow J. Benign prostatic hyperplasia: part 2 management. *BMJ* 2008; 336: 206–10.
7. Gur S, *et al.* Guide to drug therapy for lower urinary tract symptoms in patients with benign prostatic obstruction: implications for sexual dysfunction. *Drugs* 2008; 68: 209–29.
8. Speakman MJ, *et al.* Guideline for the primary care management of male lower urinary tract symptoms. *BJU Int* 2004; 93: 985–90.
9. Wang C. Phosphodiesterase-5 inhibitors and benign prostatic hyperplasia. *Curr Opin Urol* 2010; 20: 49–54.
10. Ishani A, *et al.* Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med* 2000; 109: 654–64.
11. Wilt T, *et al.* Beta-sitosterols for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 17/03/10).
12. Tacklind J, *et al.* Serenoa repens for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 17/03/10).
13. Larson TR. Rationale and assessment of minimally invasive approaches to benign prostatic hyperplasia therapy. *Urology* 2002; 59 (suppl 2A): 12–16.

Cystitis

Signs and symptoms of cystitis (inflammation of the bladder) include suprapubic pain, dysuria, frequency and urgency of urination, nocturia, and haematuria. It may have various causes but is usually associated with urinary-tract infections (see p. 213.1). Non-infectious cystitis can occur as an adverse effect of some drugs such as NSAIDs (notably tiaprofenic acid).[1] Pelvic radiotherapy and some drugs used for cancer chemotherapy can also cause haemorrhagic cystitis (below). Other inflammatory non-infectious forms of cystitis include interstitial cystitis (see p. 2348.1) and rare conditions such as eosinophilic cystitis.[2]

1. Bramble FJ, Morley R. Drug-induced cystitis: the need for vigilance. *Br J Urol* 1997; 79: 3–7.
2. Teegavarapu PS, *et al.* Eosinophilic cystitis and its management. *Int J Clin Pract* 2005; 59: 356–60.

Haemorrhagic cystitis. Haemorrhagic cystitis results from damage to the bladder wall that causes diffuse bleeding from the endothelial lining; damage may range from minor telangiectatic bleeding to diffuse necrotic ulceration.[1] Signs and symptoms include haematuria, dysuria, urgency, and increased frequency of urination.

Haemorrhagic cystitis may be associated with various diseases, drug and radiation therapies, infections, and toxins. Associated diseases include carcinoma of the bladder, rheumatoid arthritis, and amyloidosis.[1] Drugs that are often associated with haemorrhagic cystitis are antineoplastics, particularly the oxazaphosphorine alkylating agents cyclophosphamide and ifosfamide[1,2] (see also Effects on the Bladder under Cyclophosphamide, p. 772.3). Other drugs with which haemorrhagic cystitis has been reported include penicillins and NSAIDs.[2] Pelvic irradiation[3] for genito-urinary malignancies may cause acute symptoms that can occur up to 6 months after irradiation; some patients will develop chronic symptoms and in a small number the symptoms may become debilitating and refractory to conservative management. Viruses such as adenovirus, BK virus, and CMV can cause haemorrhagic cystitis, particularly in immunocompromised patients.[1,4] In some cases, bacterial or fungal infection, or parasitical infestation may be responsible.[2] Other causative agents have included toxins such as dyes, insecticides, and turpentine.[1]

Initial supportive **treatment** of haemorrhagic cystitis involves increasing fluid intake to hydrate the bladder and dilute the concentration of any toxic agent in the urine. Symptomatic relief with antispasmodics and analgesics may be indicated.[1] If haematuria does not improve or resolve, intravesical treatment may be considered. This usually begins with a continuous bladder irrigation of *sodium chloride 0.9%*, to remove existing clots.[1-3] For bleeding that persists or worsens, other treatments have been described, mostly in case reports or small series.[1-5] *Alum* irrigation has been used for its astringent properties, but its effect is rarely permanent. Adverse effects include suprapubic pain, fever, bladder spasm, and urinary retention or frequency; alum precipitation can block the catheter and aluminium toxicity may occur rarely. *Silver nitrate* instillation has a cauterising effect by coagulating proteins on the bladder mucosa, *phenol* causes a chemical cauterisation, and *formaldehyde* hydrolyses protein on the bladder wall, coagulating tissue and controlling bleeding in the mucosa and submucosa. However, the duration of effect of these cauterising agents is often short, they are contra-indicated in patients with ureteric reflux, and treatments are painful, necessitating anaesthesia. *Prostaglandins*, such as alprostadil, carboprost, and dinoprostone, have been instilled into the bladder for a cytoprotective effect, to stimulate platelet aggregation, and to cause local vasoconstriction.

There are also reports of successful systemic treatment in some cases that were refractory to intravesical therapy. *Conjugated oestrogens* have been given intravenously and orally.[1] The *antifibrinolytic drugs*, aminocaproic acid[1,2] and tranexamic acid[2] have been given intravenously and orally; aminocaproic acid has also been given intravesically. Oral

pentosan polysulfate sodium has been used in radiation-induced haemorrhagic cystitis.[3] *Hyperbaric oxygen* therapy increases tissue oxygenation and has been used particularly in radiation-induced haemorrhagic cystitis to treat radionecrosis and tissue ischaemia.[3,5] Cryosurgery using *liquid nitrogen* has been used rarely.[1] Systemic *antivirals* such as cidofovir have been used to treat virus-associated haemorrhagic cystitis after haematopoietic stem cell transplant.[4] *Clotting factors* such as eptacog alfa have also been used in haematopoietic stem cell transplant patients, although adverse effects limit use to refractory, life-threatening, acute haemorrhage.[4]

In cases that do not respond to drug treatment, *surgical* options include urinary diversion, internal iliac artery embolisation, unilateral hypogastric artery ligation, and if all else fails, cystectomy.[1-3] Hydrodistension, the application of pressure to the bladder wall by an inflated balloon, has also been used.[5] However, anaesthesia is required, its effect is short-lived, and it is associated with the risk of bladder perforation.[1,2,5]

Prophylaxis to reduce the risk of haemorrhagic cystitis associated with high-dose cyclophosphamide and ifosfamide includes intravenous hydration with diuresis, frequent voiding of the bladder or bladder catheterisation with sodium chloride 0.9% irrigation, and the use of *mesna* as a uroprotectant.[1,2] Improvements in radiotherapy techniques are reducing the risk of radiation-induced haemorrhagic cystitis.[3]

1. West NJ. Prevention and treatment of hemorrhagic cystitis. *Pharmacotherapy* 1997; 17: 696–706.
2. Traxer O, *et al.* Cystite hémorragique: étiologie et traitement. *Prog Urol* 2001; 11: 591–601.
3. Crew JP, *et al.* Radiation-induced haemorrhagic cystitis. *Eur Urol* 2001; 40: 111–23.
4. Harkensee C, *et al.* Prevention and management of BK-virus associated haemorrhagic cystitis in children following haematopoietic stem cell transplantation—a systematic review and evidence-based guidance for clinical management. *Br J Haematol* 2008; 142: 717–31.
5. Choong SKS, *et al.* The management of intractable haematuria. *BJU Int* 2000; 86: 951–9.

Interstitial cystitis. Interstitial cystitis is a chronic inflammatory condition of the bladder that mainly affects middle-aged women.[1-5] There are also rare reports of the condition occurring in children, usually girls.[6] Symptoms include perineal and pelvic pain (that is often relieved by voiding), urinary frequency, urgency, and nocturia. Interstitial cystitis is a disease of unknown aetiology and suggested possible causes have included abnormal bladder epithelial permeability, neurogenic abnormalities, autoimmune disorders, and allergic reactions with increased mast-cell activation.[1,2] It is considered to be incurable; attempts at **management** have included local and systemic drug therapy and surgery. Non-drug therapies that may be tried include exercise, stress management, bladder training, and the avoidance of foods that patients have found to exacerbate symptoms, such as caffeine, artificial sweeteners, and acidic juices.[1,2,6] However, scientific data to support these strategies are lacking.[1,6]

Oral therapy with pentosan polysulfate sodium has been given to improve the protective glycosaminoglycan layer of the bladder, and has reduced symptoms in some patients. Benefits may take more than 3 months to become apparent.[1,2] Other oral treatments that have been used for symptom relief include amitriptyline and hydroxyzine;[1-4] cimetidine[3] and gabapentin[2] have also been tried. There has been some interest in quercetin.[4]

Intravesical instillation of dimethyl sulfoxide has been shown to improve symptoms of interstitial cystitis,[1-3] although the evidence was queried by a systematic review.[5] Heparin has also been given intravesically,[1,2] as have BCG vaccine, oxybutynin, and the capsaicin analogue resiniferatoxin.[5]

Cystoscopy under anaesthesia with bladder distension, a diagnostic procedure, has been reported to relieve symptoms by destruction of the mucosal nerve plexus and tension receptors in the bladder wall. Although some[1,3,6] support its use for diagnosis and treatment, others[2] suggest that it has limited efficacy. Surgery is reserved for intractable symptoms that have failed to respond to less drastic treatments.[1]

1. Selo-Ojeme DO, Onwude JL. Interstitial cystitis. *J Obstet Gynaecol* 2004; 24: 216–25.
2. Kahn BS, *et al.* Management of patients with interstitial cystitis or chronic pelvic pain of bladder origin: a consensus report. *Curr Med Res Opin* 2005; 21: 509–16.
3. Tincello DG, Walker ACH. Interstitial cystitis in the UK: results of a questionnaire survey of members of the Interstitial Cystitis Support Group. *Eur J Obstet Gynecol Reprod Biol* 2005; 118: 91–5.
4. Theofanides TC. Treatment approaches for painful bladder syndrome/interstitial cystitis. *Drugs* 2007; 67: 215–35.
5. Dawson TE, Jamison J. Intravesical treatments for painful bladder syndrome/interstitial cystitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 17/05/10).
6. Mattox TF. Interstitial cystitis in adolescents and children: a review. *J Pediatr Adolesc Gynecol* 2004; 17: 7–11.

Diabetes insipidus

Diabetes insipidus deprives the kidney of its capacity to produce a concentrated urine, resulting in the passage of large volumes of dilute urine (polyuria) and excessive thirst (polydipsia). Patients generally have moderately raised serum-sodium concentrations but are prone to more severe hypernatraemia (p. 1778.1) when fluid is restricted.

The syndrome of diabetes insipidus is caused either:

- by a deficiency in secretion of antidiuretic hormone (ADH; vasopressin) from the posterior pituitary gland (cranial, pituitary, or neurogenic diabetes insipidus)
- or by a failure in activity of secreted ADH on renal tubules (nephrogenic diabetes insipidus)

Cranial diabetes insipidus is most commonly idiopathic (although it is now increasingly suspected to have an autoimmune basis) or occurs after surgery or trauma when it may be temporary. More rarely, it results from neoplasms, infections, or infiltrations of the CNS, or forms part of the familial DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Nephrogenic diabetes insipidus may occur as a familial X-linked recessive disorder in male infants, but is more often secondary to hypercalcaemia, hypokalaemia, or drug therapy (including lithium salts, foscarnet, and demeclocycline).

The mainstay of **diagnosis** of diabetes insipidus is measurement of serum and urine osmolality, urine specific gravity, and serum-sodium concentration. If these are found to be normal a formal water deprivation test may be performed, with careful monitoring of urine volume, osmolality, and body-weight. The test should be stopped if more than 3 litres of urine is passed or 3% of total body-weight is lost, although this is in any case virtually diagnostic of diabetes insipidus. A dose of ADH in the form of desmopressin is then given to test renal responsiveness—prompt urine concentration is indicative of cranial diabetes insipidus, while failure indicates the nephrogenic form.

Cranial diabetes insipidus is usually **treated** by replacement therapy with ADH in the form of intranasal desmopressin, although tablets are now also available and may be preferred in children; desmopressin has greater antidiuretic efficacy and considerably less vasoconstrictor activity than lypressin or vasopressin itself.

Nephrogenic diabetes insipidus is by definition unresponsive to ADH therapy and water replacement tends to be the mainstay of treatment. Thiazide diuretics, notably hydrochlorothiazide, are given with some restriction of sodium intake to patients with nephrogenic diabetes insipidus; the resultant mild sodium depletion enhances proximal renal tubular sodium and water resorption. Giving them with amiloride has been reported to have an additive effect while also preventing hypokalaemia.

Other drugs have also been tried in the management of diabetes insipidus. Chlorpropamide stimulates ADH secretion and augments the activity of residual ADH in patients with partial cranial disease and as in nephrogenic disease the thiazides may be useful. Clofibrate and carbamazepine have also been found to promote ADH secretion in these patients. Indometacin and other prostaglandin synthetase inhibitors decrease urine volume in all types of the condition. Combination of indometacin with a thiazide and desmopressin has been investigated.

References.

1. Singer I, *et al.* The management of diabetes insipidus in adults. *Arch Intern Med* 1997; 157: 1293–1301.
2. Baylis PH, Cheetham T. Diabetes insipidus. *Arch Dis Child* 1998; 79: 84–9.
3. Bendz H, Aurell M. Drug-induced diabetes insipidus. *Drug Safety* 1999; 21: 449–56.
4. Cheetham T, Baylis PH. Diabetes insipidus in children: pathophysiology, diagnosis and management. *Pediatr Drugs* 2002; 4: 785–96.
5. Sands JM, Bichet DG. Nephrogenic diabetes insipidus. *Ann Intern Med* 2006; 144: 186–94.

Erectile dysfunction

Erectile dysfunction (impotence) signifies inability of a male to achieve satisfactory erection of the penis during sexual intercourse. Estimates of prevalence depend to some extent upon the definitions that are used, but the problem is thought to be not uncommon, particularly in older men. The *causes* of erectile dysfunction may be psychological, organic, or a combination of both. Psychological factors include stress, mental depression, and anxieties about sexual performance. Organic causes include androgen deficiency as a result of hypogonadism, neurological dysfunction (including central or peripheral lesions due to malignancy or trauma), peripheral vascular disorders, and penile abnormalities such as Peyronie's disease or microphallus. Sometimes organic dysfunction may be secondary to another disease, such as diabetes mellitus in which neurological and vascular damage lead to erectile dysfunction in over one-third of all patients. In addition, erectile dysfunction may be drug-induced.

Approaches to the ***management*** of erectile dysfunction depend to some extent upon the causative factors.

In those few patients in whom erectile dysfunction is secondary to *androgen deficiency* in hypogonadism, androgen replacement, preferably by the intramuscular injection or transdermal application of a suitable testosterone ester, may be of value. Androgen replacement therapy is inappropriate in patients with normal testosterone concentrations and may carry significant health risks. In patients with hypogonadism secondary to hyperprolactinaemia addition of bromocriptine is often effective in improving sexual function.

Psychotherapy or behavioural therapy alone may be adequate in patients in whom no organic cause is detected, but even when organic factors play a role *psychosocial factors* are also important and should be addressed by appropriate counselling.

When causes of erectile dysfunction are partly or primarily *organic*, the main options are:

- use of a vacuum pump to induce erection by negative pressure, followed by constriction of the base of the penis with a band to maintain tumescence
- oral or sublingual drugs
- injection of vasoactive substances into the corpora cavernosa
- transurethral dosage of vasoactive substances
- implantation of a penile prosthesis is generally reserved for patients in whom other therapy has failed or is refused, but it may also be a suitable first-line choice for some patients

Vascular surgery may have a limited application, in vasogenic dysfunction, but its role is not clearly defined and there are some doubts about its long-term effectiveness.

Oral therapy for erectile dysfunction has had a chequered history, and most of the drugs tried have proved little more effective than placebo. However, with the advent of sildenafil and other inhibitors of phosphodiesterase type-5, oral therapy is now established in erectile dysfunction. Data from randomised controlled studies have shown efficacy of sildenafil in erectile dysfunction compared with placebo, including in men with diabetes mellitus and spinal-cord injury; it has no effect on the penis in the absence of sexual stimulation. It is generally more effective in erectile dysfunction of psychogenic origin and in mild to moderate cases of organic origin. There has, however, been concern about cardiac-related deaths associated with the use of sildenafil, although causality has not been firmly established. Visual disturbances and sudden hearing loss have also been reported. Other phosphodiesterase type-5 inhibitors also used are avanafil, tadalafil, and vardenafil.

Yohimbine, an α_2-adrenoceptor antagonist, may have some benefit, although more in erectile dysfunction of psychological than organic origin. Oral phentolamine is available for the treatment of erectile dysfunction in some countries and has been reported to be of benefit. Trazodone, a serotonin antagonist and reuptake inhibitor used in the treatment of depression, may rarely cause priapism and has therefore been investigated for the treatment of erectile dysfunction. Beneficial effects have been reported either alone or with yohimbine. Oral L-arginine, the precursor of nitric oxide, has also shown some promise in studies.

Sublingual apomorphine, a dopaminergic (D_1 or D_2) agonist, has also shown efficacy, but nausea may be a problem.

Intracavernosal injection therapy is the most effective pharmacological method of treating erectile dysfunction and, until the advent of effective oral therapy, was the most widely used. Unfortunately, one major disadvantage of this method is the need for repeated self-injection of the penis, and studies suggest that the long-term drop-out rate is high. However, it is still a valuable option in men unresponsive to, or unable to take, oral therapy. The drugs most commonly used are alprostadil, papaverine, and phentolamine. Alprostadil is preferred because it is more effective than papaverine (with or without phentolamine), and is associated with a lower incidence of priapism and fibrosis. However, the erection is frequently painful. Papaverine, a non-specific phosphodiesterase inhibitor, has been used alone or with phentolamine, an α-adrenoceptor antagonist. Erectile dysfunction of neurogenic or psychogenic origin generally responds better to papaverine than dysfunction of vascular origin. However, long-term use of intracavernosal papaverine may result in fibrosis, and it has been suggested that it should not be used more than three times a week or on two successive days. Priapism may also be a problem. Triple therapy, involving the combination of alprostadil, papaverine, and phentolamine, has been reported to be effective and to have a relatively low incidence of adverse effects. Other drugs that have been used for intracavernosal therapy include aviptadil (a smooth muscle relaxant used with phentolamine), ketanserin used with alprostadil, and moxisylyte.

The **transurethral route** is a less invasive but also less effective option than intracavernosal therapy. A transurethral pellet of alprostadil is reported to be effective, although efficacy is inconsistent; common adverse effects include penile pain and urethral pain or burning. Transurethral alprostadil as a cream or gel has also shown promise.

A number of studies have also investigated **transcutaneous** therapy. Results from pilot studies investigating transcutaneous delivery of glyceryl trinitrate, papaverine, minoxidil, or alprostadil from creams, gels, or pastes have been variable. Topical treatment with a cream containing codergocrine mesilate, isosorbide dinitrate, and either aminophylline or testosterone has also been tried, with mixed results.

References.

1. Morgentaler A. Male impotence. *Lancet* 1999; 354: 1713–18.
2. Lue TF. Erectile dysfunction. *N Engl J Med* 2000; 342: 1802–13.
3. Ralph D, McNicholas T. UK management guidelines for erectile dysfunction. *BMJ* 2000; 321: 499–503. Also available at: http://bmj.bmjjournals.com/cgi/reprint/321/7259/499.pdf (accessed 19/05/06)
4. Dey J, Shepherd MD. Evaluation and treatment of erectile dysfunction in men with diabetes mellitus. *Mayo Clin Proc* 2002; 77: 276–82.
5. Guay AT, *et al.* American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of male sexual dysfunction: a couple's problem—2003 update. *Endocr Pract* 2003; 9: 77–95. Also available at: http://www.aace.com/pub/pdf/guidelines/sexdysguid.pdf (accessed 14/06/06)
6. Jackson G. Treatment of erectile dysfunction in patients with cardiovascular disease: guide to drug selection. *Drugs* 2004; 64: 1533–45.
7. Russell ST, *et al.* Erectile dysfunction and cardiovascular disease. *Mayo Clin Proc* 2004; 79: 782–94.
8. Basu A, Ryder REJ. New treatment options for erectile dysfunction in patients with diabetes mellitus. *Drugs* 2004; 64: 2667–88.
9. Anonymous. New oral drugs for erectile dysfunction. *Drug Ther Bull* 2004; 42: 49–52.
10. Ramos AS, Samsó JV. Specific aspects of erectile dysfunction in spinal cord injury. *Int J Impot Res* 2004; 16 (suppl): S42–S45.
11. Wespes E, *et al.* European Association of Urology guidelines on erectile dysfunction (update March 2005). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/Erectile%20Dysfunction.pdf (accessed 02/09/08)
12. Montague DK, *et al.* American Urological Association. Chapter 1: the management of erectile dysfunction: an AUA update. *J Urol (Baltimore)* 2005; 174: 230–9. Also available at: http://www.auanet.org/guidelines/edmgmt.cfm (accessed 29/11/05)
13. Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? *Drugs* 2005; 65: 1621–50.
14. McMahon CN, *et al.* Treating erectile dysfunction when PDE5 inhibitors fail. *BMJ* 2006; 332: 589–92.
15. Sivalingam S, *et al.* An overview of the diagnosis and treatment of erectile dysfunction. *Drugs* 2006; 66: 2339–55.
16. Barry JM. Treating erectile dysfunction in renal transplant recipients. *Drugs* 2007; 67: 975–83.
17. Vardi M, Nini A. Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 18/06/08).
18. Miles CL, *et al.* Interventions for sexual dysfunction following treatments for cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 18/06/08).
19. McVary KT. Erectile dysfunction. *N Engl J Med* 2007; 357: 2472–81.
20. Gur S, *et al.* Guide to drug therapy for lower urinary tract symptoms in patients with benign prostatic obstruction: implications for sexual dysfunction. *Drugs* 2008; 68: 209–29.
21. Hatzimouratidis K, Hatzichristou DG. Looking to the future for erectile dysfunction therapies. *Drugs* 2008; 68: 231–50.
22. Tsertsvadze A, *et al.* Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. *Ann Intern Med* 2009; 151: 650–61.

Glomerular kidney disease

For a description of the various forms of glomerular kidney disease and their management, see p. 1604.3.

Malignant neoplasms

Malignant neoplasms of the bladder are relatively common malignancies in the developed world; the management of bladder cancer is discussed on p. 700.2. Prostate cancer is one of the most common malignancies in men and a leading cause of cancer death; its management is covered on p. 712.3. For malignancies of the kidney see p. 708.3.

Micturition disorders

Normal micturition (awareness of the need to void urine as a result of bladder filling, postponement of urination until convenient, and the ability to empty the bladder voluntarily) is controlled by the detrusor muscle of the bladder (smooth muscle innervated mainly by parasympathetic nerves) and the external sphincter (sympathetic innervation). During urination parasympathetic stimulation causes the detrusor muscle to contract while reduced sympathetic tone allows the external sphincter to relax. Micturition disorders can occur through local effects on the bladder or urethra or may result through disturbances of their nervous control. They include nocturnal enuresis, urinary incontinence, and urinary retention. The terms 'neurogenic bladder' and 'neuropathic bladder' are used loosely to describe any bladder dysfunction resulting from neurological disturbance.

Nocturnal enuresis. Involuntary discharge of urine during sleep, termed nocturnal enuresis (bed-wetting), is a normal occurrence in young children, but may persist in up to 5% by the age of 10 years. Nocturnal enuresis is defined as primary if there has never been a period of dryness for more than 6 months, and secondary if the child was dry for such a period before the onset of bed-wetting.

Nonpharmacological approaches to **treatment** include bladder retention training, motivational therapy, and behaviour modification or conditioning therapy using moisture-sensitive alarms. Drug therapy may initially produce a more rapid response, but training and the use of alarms has generally appeared to be more effective and to have a lower relapse rate. The *BNFC* states that, for children under 5 years of age, reassurance and advice on the management of nocturnal enuresis can be useful for some families; drug therapy may be considered in children over 5 years depending on their maturity and motivation, the frequency of bed-wetting, and the needs of the child and their family. Drug therapy is probably most useful for intermittent use on special occasions such as sleeping away from home or when added to treatment in children who fail to respond to nonpharmacological methods alone. The long-term use of drugs for enuresis is controversial.

- Use of oral *desmopressin* at night can be effective in the short-term control of nocturnal enuresis and many now consider it to be the drug of choice in terms of safety. However, it should not be given when enuresis is due to polydipsia as desmopressin may provoke water intoxication and convulsions due to hyponatraemia.
- Tricyclic antidepressants have also been used and of these most experience has been with *imipramine*. Their mechanism of action in nocturnal enuresis is unclear. It may be partly the result of their antimuscarinic and antispasmodic actions.
- Antimuscarinics such as *oxybutynin* reduce uninhibited bladder contractions, but although they may be of benefit in diurnal enuresis they are rarely of benefit in nocturnal enuresis alone. Combination with desmopressin may improve response in some cases.

References.

1. Evans JHC. Evidence based management of nocturnal enuresis. *BMJ* 2001; 323: 1167–9. Correction. *ibid.* 2002; 324: 98.
2. Glazener CMA, Evans JHC. Desmopressin for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 29/11/05).
3. Glazener CMA, *et al.* Tricyclic and related drugs for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 29/11/05).
4. Glazener CMA, *et al.* Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 29/11/05).
5. Anonymous. Management of bedwetting in children. *Drug Ther Bull* 2004; 42: 33–7.
6. Müller D, *et al.* Comparative tolerability of drug treatment for nocturnal enuresis in children. *Drug Safety* 2004; 27: 717–27.
7. Hjalmas K, *et al.* Nocturnal enuresis: an international evidence based management strategy. *J Urol (Baltimore)* 2004; 171: 2545–61.
8. Fritz G, *et al.* American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with enuresis. *J Am Acad Child Adolesc Psychiatry* 2004; 43: 1540–50. Also available at: http://www.aacap.org/galleries/PracticeParameters/Enuresis.pdf (accessed 02/09/08)
9. Glazener CMA, *et al.* Alarm interventions for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 29/11/05).
10. Robson WLM. Evaluation and management of enuresis. *N Engl J Med* 2009; 360: 1429–36.
11. NICE. Nocturnal enuresis: the management of bedwetting in children and young people (issued October 2010). Available at: http://www.nice.org.uk/nicemedia/live/13246/51367/51367.pdf (accessed 18/11/10)

Urinary incontinence and retention. Urinary incontinence is defined as an involuntary loss of urine that is objectively demonstrable and a social or hygienic problem. Nocturnal enuresis in children is discussed above. Depending on the cause patients may have symptoms of urinary frequency, nocturia, urgency, dribbling, or dysuria. Classifications of incontinence vary but the main types include: stress incontinence, urge incontinence and overactive bladder, and overflow incontinence (a consequence of urinary retention). Patients may also have mixed types, for example combined stress and urge incontinence. The term functional incontinence is used when the patient's condition is due to impaired mobility or mental function. It is important to determine the type and, where possible, cause of urinary incontinence before attempting treatment. Urinary-tract infections, constipation, and benign prostatic hyperplasia may mimic or cause the symptoms of urinary incontinence and should be excluded.

Stress incontinence is the commonest form of incontinence in women; some men may also develop stress incontinence e.g. after prostatectomy. The patient usually has urethral sphincter incompetence and loss of urine is associated with increases in intra-abdominal pressure such as may occur on standing or coughing. Initial management should be conservative: first-line treatment is likely to be pelvic floor exercises; other treatments may include electrical stimulation or biofeedback, the use of devices such as vaginal cones, surgery, or drugs.

- Drug therapy has had only a secondary role in the treatment of stress incontinence although the serotonin and noradrenaline reuptake inhibitor *duloxetine* is now licensed in several countries to increase urethral tone in the treatment of moderate to severe stress urinary incontinence, and may be an alternative to surgical treatment. Alpha-adrenoceptor agonists such as *ephedrine, phenylpropanolamine,* and *pseudoephedrine* have been used to increase tone in the muscles of the urethra and at the base of the bladder; they may prevent incontinence in certain stress situations, but long-term experience has been mostly disappointing. *Oestrogens* used with an alpha-adrenoceptor agonist such as phenylpropanolamine appear to be effective and may be of use for postmenopausal women with mild stress incontinence; unfortunately, addition of a progestogen (necessary in women with an intact uterus) might exacerbate the incontinence. The value of oestrogens used without an alpha-adrenoceptor agonist is less clear. Intra-urethral injections of *collagen* or *polytef* appear to be effective, but there are concerns over migration and granuloma formation with polytef.

In **urge incontinence**, also known as unstable bladder or detrusor instability, contractions of the detrusor muscle occur without warning and overcome urethral sphincter resistance, despite any attempt the patient might make to prevent it. Urge incontinence is the most common form of incontinence in the elderly and is often refractory to treatment. The cause is usually unknown and these cases are referred to as being due to **idiopathic detrusor instability**. When there is overt neurological disease, such as upper motor neurone lesions in spinal cord injury or multiple sclerosis, the term **detrusor hyperreflexia** is used. **Overactive bladder syndrome** is defined as urgency (a compelling desire to urinate) with or without actual urge incontinence; patients usually exhibit urinary frequency and nocturia. In men it is sometimes associated with benign prostatic hyperplasia (p. 2347.1).

Reduction of excessive fluid intake and avoidance of drinks containing alcohol or caffeine may control mild symptoms of urge incontinence or overactive bladder. Behavioural therapy may be helpful: bladder training for at least 6 weeks is a first-line option in women with urge or mixed incontinence. Women with mixed incontinence may also benefit from pelvic floor exercises. Other treatments that have been tried include hypnotherapy, acupuncture, and biofeedback.

- No drug treatment has been found to be universally effective. Drugs with antimuscarinic activity can be of significant clinical benefit. They inhibit unstable detrusor muscle contractions but the incidence of adverse effects can be high. As these drugs can increase bladder volume they should not be used in patients with urinary retention. The antimuscarinic *oxybutynin* also has direct smooth muscle relaxant properties and has been widely used, but adverse effects are common. Transdermal or extended-release formulations may be considered in women who cannot tolerate conventional formulations of oxybutynin. *Tolterodine, trospium,* and *propiverine* are other alternatives. (In the UK, propiverine is suggested for overactive bladder but not for incontinence.) *Fesoterodine* is also available for the management of overactive bladder syndrome. Selective M_3 antimuscarinics, *darifenacin* and *solifenacin,* may also be considered. They appear to be at least as effective as less selective antimuscarinics. The older antimuscarinics *flavoxate, propantheline,* and *emepronium* are not now recommended.

  Mirabegron, a beta$_3$-adrenoceptor agonist, is available in some countries for the management of overactive bladder syndrome. *Tricyclic antidepressants* have also been used in urge incontinence because of their antimuscarinic activity but their main use has been in nocturnal enuresis and nocturia (see above). *Desmopressin* is also mainly used in nocturnal enuresis and nocturia. Evidence for *oestrogens* is inconclusive, but they may be useful as adjuncts in postmenopausal women with vaginal atrophy and symptoms of urgency, frequency, and nocturia. Injection of *botulinum A toxin* into the detrusor muscle may be effective in the treatment of detrusor hyperreflexia that is resistant to antimuscarinics. Sacral nerve stimulation, using an implantable device, may be an option in cases that are resistant to drug treatment. Surgery is reserved for intractable cases.

Urge incontinence can also be due to abnormalities in bladder sensation; the causes of **sensory urgency** are often unknown but may be due to conditions such as urinary-tract infections or interstitial cystitis. Bladder retraining techniques and antimuscarinic therapy have been suggested when no underlying disorder can be identified.

Patients with **overflow incontinence** suffer from a continuous or frequent dribbling of urine as a consequence of an overdistended bladder produced by **urinary retention.** It may result from some form of urethral blockage or may be associated with drug treatment or conditions that reduce detrusor contractions or interfere with relaxation of the urethra. Overflow incontinence is uncommon in women and most patients are elderly men with urethral blockage due to benign prostatic hyperplasia (p. 2347.1). However, urinary retention may also occur postpartum or postoperatively. Treatment depends on the underlying condition. Catheterisation is used to relieve acute painful urinary retention or when no cause can be

found. Surgical procedures or dilatation are often used to correct any mechanical outflow obstruction.

- Alpha-adrenoceptor blocking drugs such as *alfuzosin, doxazosin, indoramin, prazosin, tamsulosin,* and *terazosin* may be given to patients waiting for surgery or to those unfit for surgery. They decrease outflow resistance and improve bladder emptying. Patients with detrusor hypotonicity have been given parasympathomimetics such as *bethanechol, carbachol,* and *distigmine* to increase detrusor muscle contractions but there have been doubts about their efficacy and safety. Use of parasympathomimetics for postoperative urinary retention has been superseded by catheterisation.

References.

1. Scientific Committee of the First International Consultation on Incontinence. Assessment and treatment of urinary incontinence. *Lancet* 2000; 355: 2153–8.
2. Couture JA, Valiquette L. Urinary incontinence. *Ann Pharmacother* 2000; 34: 646–55.
3. Thakar R, Stanton S. Management of urinary incontinence in women. *BMJ* 2000; 321: 1326–31.
4. Haeusler G, *et al.* Drug therapy of urinary urge incontinence: a systematic review. *Obstet Gynecol* 2002; 100: 1003–16.
5. Anonymous. Managing lower urinary tract symptoms in men. *Drug Ther Bull* 2003; 41: 18–21.
6. Ellerkmann RM, McBride A. Management of obstructive voiding dysfunction. *Drugs Today* 2003; 39: 513–40.
7. Ouslander JG. Management of overactive bladder. *N Engl J Med* 2004; 350: 786–99.
8. Hakroyd-Leduc JM, Straus SE. Management of urinary incontinence in women: scientific review. *JAMA* 2004; 291: 986–95.
9. Scottish Intercollegiate Guidelines Network. Management of urinary incontinence in primary care: a national clinical guideline (December 2004). Available at: http://www.sign.ac.uk/pdf/sign79.pdf (accessed 29/11/05)
10. Zinner NR, *et al.* Pharmacotherapy for stress urinary incontinence: present and future options. *Drugs* 2004; 64: 1503–16.
11. Hashim H, Abrams P. Drug treatment of overactive bladder: efficacy, cost and quality-of-life considerations. *Drugs* 2004; 64: 1643–56.
12. Sutherland SE, Goldman HB. Treatment options for female urinary incontinence. *Med Clin North Am* 2004; 88: 345–66.
13. Thomas DR. Pharmacologic management of urinary incontinence. *Clin Geriatr Med* 2004; 20: 511–23.
14. American College of Obstetricians and Gynecologists. Urinary incontinence in women. *Obstet Gynecol* 2005; 105: 1533–45.
15. Alhasso A, *et al.* Adrenergic drugs for urinary incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 29/11/05).
16. Hay-Smith J, *et al.* Which anticholinergic drug for overactive bladder symptoms in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 29/11/05).
17. Badawi JK, Langbein S. Selective beta-adrenoceptor agonists, calcium antagonists and potassium channel openers as a possible medical treatment of the overactive bladder and urge incontinence. *Pharmazie* 2006; 61: 175–8.
18. Staskin DR, MacDiarmid SA. Pharmacologic management of overactive bladder: practical options for the primary care physician. *Am J Med* 2006; 119 (suppl 1): 24–8.
19. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)
20. Appell RA. Pharmacotherapy for overactive bladder: an evidence-based approach to selecting an antimuscarinic agent. *Drugs* 2006; 66: 1361–70.
21. Norton P, Brubaker L. Urinary incontinence in women. *Lancet* 2006; 367: 57–67.
22. Hashim H, Abrams P. Pharmacological management of women with mixed urinary incontinence. *Drugs* 2006; 66: 591–606.
23. Schurch B. Botulinum toxin for the management of bladder dysfunction. *Drugs* 2006; 66: 1301–18.
24. Alhasso AA, *et al.* Anticholinergic drugs versus non-drug active therapies for overactive bladder syndrome in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 24/06/08).
25. Nabi G, *et al.* Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 24/06/08).
26. Gibbs CF, *et al.* Office management of geriatric urinary incontinence. *Am J Med* 2007; 120: 211–20.
27. Duthie J, *et al.* Botulinum toxin injections for adults with overactive bladder syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 24/06/08).
28. Roxburgh C, *et al.* Anticholinergic drugs versus other medications for overactive bladder syndrome in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/06/08).
29. Anonymous. Update on drugs for overactive bladder syndrome. *Drug Ther Bull* 2007; 45: 44–8.
30. Aning JJ, *et al.* Management of acute urinary retention. *Br J Hosp Med* 2007; 68: 408–11.
31. Barendrecht MM, *et al.* Is the use of parasympathomimetics for treating an underactive urinary bladder evidence-based? *BJU Int* 2007; 99: 749–52.
32. Shamliyan TA, *et al.* Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. *Ann Intern Med* 2008; 148: 459–73.
33. Rogers RG. Urinary stress incontinence in women. *N Engl J Med* 2008; 358: 1029–36.
34. Verhamme KMC, *et al.* Drug-induced urinary retention: incidence, management and prevention. *Drug Safety* 2008; 31: 373–88.
35. Novara G, *et al.* A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. *Eur Urol* 2008; 54: 740–63.
36. Schröder A, *et al.* European Association of Urology. Guidelines on urinary incontinence (updated April 2010). Available at: http://www.uroweb.org/gls/pdf/16_Urinary_Incontinence%202010.pdf (accessed 03/10/11)
37. Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 21/10/11).

Premature ejaculation

A universally accepted definition of premature ejaculation has not yet been established, but the American Urological Association has defined it as ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.[1]

Management may include psychological, behavioural, and drug treatment.[1] Several antidepressants have been evaluated for a therapeutic effect in premature ejaculation,[1-3] based on their adverse effects of anorgasmia and delayed ejaculation. The SSRIs fluoxetine, paroxetine, and sertraline, and the tricyclic antidepressant clomipramine, have been used successfully. However, the optimal dosing regimen for these drugs has not been established, and they have been given either on a continuous daily basis or as single doses only before intercourse. Doses that have been effective in premature ejaculation have usually been lower than those recommended for the treatment of depression. A rapidly absorbed short-acting SSRI, dapoxetine, is used specifically for on-demand treatment of premature ejaculation. Topical anaesthetics, such as lidocaine/prilocaine cream, have been applied to the penis to delay ejaculation.[1-3] Disadvantages of this therapy include loss of erection due to numbness associated with prolonged application, and numbness in the partner caused by residual topical anaesthetic.[1,3] Available commercial preparations intended for such use include benzocaine gels and lidocaine sprays. Sildenafil, a phosphodiesterase type-5 inhibitor used for erectile dysfunction, has also been tried with some success;[1] however, some consider that such drugs should only be used in patients with co-morbid erectile dysfunction.[3]

1. American Urological Association. Erectile Dysfunction Guideline Update Panel. AUA guideline on the pharmacologic management of premature ejaculation. *J Urol (Baltimore)* 2004; 172: 290–4. Also available at: http://www.auanet.org/guidelines/pe.cfm (accessed 29/11/05)
2. Waldinger MD. Lifelong premature ejaculation: from authority-based to evidence-based medicine. *BJU Int* 2004; 93: 201–7.
3. Waldinger MD. Premature ejaculation: definition and drug treatment. *Drugs* 2007; 67: 547–68.

Prostatitis

The term prostatitis is used to describe several clinical syndromes, including well-defined bacterial infections of the prostate gland, poorly-defined chronic pelvic pain, and asymptomatic inflammation of the prostate. Prostatitis is relatively common as a urological diagnosis, with about 30% of men having such symptoms at some time in their life.[1] The US National Institutes of Health classification system[1,2] for prostatitis consists of categories:

- I: acute bacterial prostatitis
- II: chronic bacterial prostatitis
- III: chronic prostatitis/chronic pelvic pain syndrome (subdivided into IIIA inflammatory and IIIB non-inflammatory)
- IV: asymptomatic inflammatory prostatitis

Acute bacterial prostatitis (category I) is most often due to Gram-negative pathogens, particularly *Escherichia coli* and other enterobacteriaceae. Symptoms include fever, chills, malaise and myalgia, with rectal, low back, or perineal pain. There is often bacteriuria with frequent and urgent dysuria. The prostate is enlarged, tender, and warm.[1-3] **Chronic bacterial prostatitis** (category II) is relatively rare, and may develop from acute bacterial prostatitis in some men. It is characterised by pelvic pain and recurrent urinary-tract infections. The prostate appears to be normal but in some cases is swollen or firm.[1] Bacterial prostatitis should be managed with appropriate antibacterial therapy[2-5] (see under Urinary-tract Infections, p. 213.1).

Chronic prostatitis/chronic pelvic pain syndrome (category III), which has also been described as abacterial prostatitis, is the most common form of prostatitis. The aetiology and pathogenesis remain unclear, and suggestions have included infection with atypical organisms that cannot be detected by conventional techniques, intraprostatic reflux, or immunological processes.[1] Neurological[6] or psychological factors[1,6] may also play a role in some patients. Symptoms of chronic pelvic pain syndrome include pelvic, perineal, and genital pain, lower urinary-tract symptoms, sexual dysfunction, and general symptoms such as headache and fatigue.[1,3] In inflammatory chronic pelvic pain syndrome (category IIIA), leucocytes can be found in expressed prostatic secretion, in the urine after prostatic massage, and in semen; no leucocytes can be detected in non-inflammatory chronic pelvic pain syndrome (category IIIB; previously called prostatodynia).[1,3,6]

There are no universally effective treatments for chronic pelvic pain syndrome; overall, studies of treatments have been small and of poor quality.[2,5-7] Many clinicians favour initial management with antibacterials despite negative cultures, in order to treat occult atypical infection.[2] An oral fluoroquinolone is the antibacterial of choice (or a tetracycline for patients allergic to fluoroquinolones). Recommended duration of treatment varies, but courses are generally of 4 to 8 weeks, depending on response in the first few weeks.[3,4,6] However, there is no strong evidence to support this practice,[2,7] and although there are some studies to suggest that antibacterial treatment may be beneficial in inflammatory chronic pelvic pain syndrome, there is less evidence for the non-inflammatory form.[4] Other treatments that have been tried, with variable results, include[2,3,5-9] the 5α-reductase inhibitor finasteride, alpha blockers such as alfuzosin, terazosin, or tamsulosin, fluoxetine, pentosan polysulfate sodium, mepartricin, pollen extract, quercetin, and NSAIDs. The role of allopurinol is controversial. Non-drug treatments that have shown some promise include transurethral or transrectal microwave thermotherapy[3-7] and sacral nerve stimulation.[6] Drugs used for symptomatic relief of neuropathic pain may include tricyclic antidepressants such as amitriptyline, or antiepileptics such as gabapentin. Anticholinergics such as oxybutynin or tolterodine may be used for urinary frequency.[6]

Asymptomatic inflammatory prostatitis (category IV) is often detected coincidentally during examination for other disorders.[1]

1. Schneider H, *et al.* Prostate-related pain in patients with chronic prostatitis/chronic pelvic pain syndrome. *BJU Int* 2005; 95: 238–43.
2. British Association for Sexual Health and HIV Clinical Effectiveness Group. United Kingdom national guideline for the management of prostatitis (2008). Available at: http://www.bashh.org/guidelines (accessed 09/04/10)
3. Murphy AB, *et al.* Chronic prostatitis: management strategies. *Drugs* 2009; 69: 71–84.
4. Wagenlehner FME, Naber KG. Prostatitis: the role of antibiotic treatment. *World J Urol* 2003; 21: 105–8.
5. Schaeffer AJ. Chronic prostatitis and the chronic pelvic pain syndrome. *N Engl J Med* 2006; 355: 1690–8.
6. Pontari MA. Chronic prostatitis/chronic pelvic pain syndrome in elderly men: toward better understanding and treatment. *Drugs Aging* 2003; 20: 1111–25.
7. Collins MM, *et al.* Diagnosis and treatment of chronic abacterial prostatitis: a systematic review. *Ann Intern Med* 2000; 133: 367–81.
8. Mishra VC, *et al.* Role of alpha-blockers in type III prostatitis: a systematic review of the literature. *J Urol (Baltimore)* 2007; 177: 25–30.
9. Nickel JC, *et al.* Chronic Prostatitis Collaborative Research Network. Alfuzosin and symptoms of chronic prostatitis-chronic pelvic pain syndrome. *N Engl J Med* 2008; 359: 2663–73.

Renal calculi

The solubility of calcium, oxalate, and phosphate in normal urine is maintained by a variety of inhibitors of crystallisation, both organic and inorganic. However, increases in the concentrations of crystalline substances in the urine, or decreases in the relative proportions of crystallisation inhibitors, may render individuals susceptible to urolithiasis, the formation of renal calculi (kidney stones). Renal calculi consist of crystalline components arranged around an organic matrix. They are typically formed in the calices or renal pelvis, and may become lodged in the ureter. Calcium-containing stones (usually calcium oxalate and calcium phosphate in variable proportions) account for the vast majority of occurrences although stones of other compositions including cystine, uric acid, or magnesium ammonium phosphate (also called struvite or infection stones), are occasionally seen.

The incidence and prevalence of renal calculi is increasing.[1,2] The lifetime risk of stone development varies between populations but is about 15% for white men and 6% for white women, with a lifetime recurrence rate of up to 50%.[3] Risk factors include obesity, low fluid intake, and a diet high in protein, refined carbohydrates, and salt.[1] Some conditions can promote calculi formation, including renal tubular acidosis, primary hyperparathyroidism, sarcoidosis, primary hyperoxaluria, inflammatory bowel disease, hyperuricaemic conditions, and cystic fibrosis.[4] Drug-induced calculi can be formed by crystallisation of poorly soluble drugs with a high urinary excretion, or by an effect on calcium oxalate or purine metabolism.[5]

Treatment. Most renal calculi are small, and stones that are less than 5 mm in diameter will usually pass spontaneously.[6-9] Patients may be asymptomatic or may pass small stones with relatively little discomfort, but passage of a larger stone down the ureter can be accompanied by excruciating pain (renal or ureteral colic) requiring analgesia (see Biliary and Renal Colic, p. 6.3). If there is no obstruction, infection, or other complication, conservative treatment is favoured, with the patient being monitored radiographically over several weeks to see if the stone will pass of its own accord.[10]

There is some interest in the possible use of drug treatment to ease the spontaneous passage of the stone. Small studies using a calcium-channel blocker (usually nifedipine) or an alpha$_1$-adrenoceptor blocker such as tamsulosin, sometimes with a corticosteroid such as deflazacort, have reported improvements in the rate of stone expulsion and expulsion time, and reductions in analgesic requirements, in patients with uncomplicated lower ureteral stones. A meta-analysis[11] of 9 studies confirmed the apparent benefit of such treatment, and a further meta-analysis[12] of 11 studies using alpha blockers in particular, found that patients had a 44% greater likelihood

of spontaneous stone passage than those not given these drugs. Although a suitable randomised controlled study is required to confirm efficacy, medical treatment may offer a viable alternative to lithotripsy or ureteroscopy.[11] A literature review[13] suggested that daily doses of nifedipine 30 mg, doxazosin 4 mg, tamsulosin 400 micrograms, or terazosin 5 mg given for 28 to 45 days are effective in enhancing expulsion of ureteral stones that are less than 15 mm in diameter. Another[14] considered alpha blockers to be more effective than calcium-channel blockers; little benefit was noted in small studies where a corticosteroid or an antimuscarinic was added to an alpha blocker.

Where intervention is considered necessary for stone removal the choice of technique depends on the size, composition, and location of the stone. Extracorporeal shock wave lithotripsy is generally favoured, but other procedures such as ureteroscopy or percutaneous nephrolithotomy are used for more complex cases.[7,8,15] Antibacterials may be needed for infection (see Urinary-tract Infections, p. 213.1).

Prevention. In the prevention of recurrence it is important to identify, and where possible correct, any underlying disease process or biochemical or anatomical abnormality. Certain general measures are also appropriate. Patients should drink at least 2 to 3 litres of fluid daily in order to maintain an adequate volume of urine.[1,3,7,16] In hot climates or working environments a higher volume of fluid should be taken.

In preventing the recurrence of **calcium stones**, a balanced diet that is low in protein and salt[1,3,10,17] and high in fibre[1,7] is generally advocated. In the past patients were advised to decrease their calcium intake, but studies have found an inverse relationship between dietary calcium intake and stone formation.[3,7,16,17] Also, because oxalate is bound by calcium in the gut, preventing its absorption, a low calcium intake can increase oxalate absorption and the risk of stone formation. Therefore, a normal level of dietary intake of calcium is now advised[1,3,7,17,18] (an exception to this is in patients with absorptive hypercalciuria type I, a rare condition of intestinal calcium hyperabsorption).[1] However, calcium supplements appear to increase the risk of stone formation and are generally avoided.[3,7,17] If they are used, they should be taken with meals to avoid hypercalciuria.[1,18] Excessive dietary oxalate intake should also be avoided;[3,7,10,17] foods containing large quantities of bioavailable oxalate include spinach, rhubarb, nuts, and cocoa.[17]

Where pharmacological therapy is indicated, choice of treatment depends on the underlying metabolic abnormality and stone composition. Alkaline citrate, usually given as potassium citrate, is commonly used to prevent the recurrence of calcium stones. It acts as a urinary alkaliniser and increases citrate excretion; citrate forms complexes with calcium to reduce urinary saturation of calcium salts and inhibits crystallisation.[2,7,16,18] Potassium citrate is the main treatment option in patients with hypocitraturia and renal tubular acidosis.[1,3,7] In hypercalciuria, a thiazide diuretic or indapamide can also be used to increase distal tubular calcium reabsorption;[1-3,6,7,10,16,19] potassium citrate can also prevent diuretic-induced hypokalaemia in these patients. In the prevention of calcium stones with hyperoxaluria, a restriction of oxalate-rich food and an adequate dietary calcium intake (or calcium supplements taken with meals) are advocated.[6,10,17,18] The use of magnesium has also been suggested[1] although it may be no better than placebo.[3,7] Some patients with primary hyperoxaluria may respond to high doses of pyridoxine.[1,3,7,10,18] In hyperuricosuria, reduced purine intake and allopurinol may be effective.[1,3,7,10]

Prevention of **uric acid stones** is based on adequate fluid intake, a low purine diet, and urinary alkalinisation with potassium citrate. Allopurinol may be used if there are high levels of urate.[1-3,6,7] Acetazolamide has been used short term.[6]

Struvite stones are caused by urease-producing bacteria. Antibacterials are used, and may be required long term, with urinary acidification using ammonium chloride[7] or methionine.[1,7] Dietary phosphate restriction may also be appropriate for patients with phosphate excretion of more than 35 mmol/day.[1] Acetohydroxamic acid, an inhibitor of bacterial urease, may be used as an adjunct in selected cases of severe infection,[7] but its use has been limited by adverse effects.[3,10]

Cystine stones are associated with cystinuria, see p. 1567.2.

1. Straub M, Hautmann RE. Developments in stone prevention. *Curr Opin Urol* 2005; **15**: 119–26.
2. Moe OW. Kidney stones: pathophysiology and medical management. *Lancet* 2006; **367**: 333–44.
3. Reynolds TM. Chemical pathology clinical investigation and management of nephrolithiasis. *J Clin Pathol* 2005; **58**: 134–40.
4. Matlaga BR, Assimos DG. Urologic manifestations of nonurologic disease: urolithiasis. *Urol Clin North Am* 2003; **30**: 91–9.
5. Daudon M, Jungers P. Drug-induced renal calculi: epidemiology, prevention and management. *Drugs* 2004; **64**: 245–75.
6. Bihl G, Meyers A. Recurrent renal stone disease—advances in pathogenesis and clinical management. *Lancet* 2001; **358**: 651–6.
7. Tiselius H-G, *et al.* European Association of Urology guidelines on urolithiasis (update March 2008). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/Urolithiasis.pdf (accessed 02/09/08)
8. Anagnostou T, Tolley D. Management of ureteric stones. *Eur Urol* 2004; **45**: 714–21.
9. Miller NL, Lingeman JE. Management of kidney stones. *BMJ* 2007; **334**: 468–72.
10. Parmar MS. Kidney stones. *BMJ* 2004; **328**: 1420–4.
11. Hollingsworth JM, *et al.* Medical therapy to facilitate urinary stone passage: a meta-analysis. *Lancet* 2006; **368**: 1171–9.
12. Parsons JK, *et al.* Efficacy of α-blockers for the treatment of ureteral stones. *J Urol (Baltimore)* 2007; **177**: 983–7.
13. Beach MA, Mauro LS. Pharmacologic expulsive treatment of ureteral calculi. *Ann Pharmacother* 2006; **40**: 1361–8.
14. Tzortzis V, *et al.* Medical expulsive therapy for distal ureteral stones. *Drugs* 2009; **69**: 677–92.
15. Preminger GM, *et al.* American Urological Association. AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. *J Urol (Baltimore)* 2005; **173**: 1991–2000. Also available at: http://www.auanet.org/guidelines/staghorncalculi05.cfm (accessed 29/11/05)
16. Pearle MS. Prevention of nephrolithiasis. *Curr Opin Nephrol Hypertens* 2001; **10**: 203–9.
17. Baker MJ, Longyhore DS. Dietary calcium, calcium supplements, and the risk of calcium oxalate kidney stones. *Am J Health-Syst Pharm* 2006; **63**: 772–5.
18. Tiselius H-G. Epidemiology and medical management of stone disease. *BJU Int* 2003; **91**: 758–67.
19. Pearle MS, *et al.* Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* 1999; **13**: 679–85.

Renal colic

For the treatment of urological pain see Biliary and Renal Colic, p. 6.3.

Renal failure

For discussions of acute and chronic renal failure and their management, see p. 1779.1.

Sexually transmitted diseases

For discussion of sexually transmitted diseases and their treatment see p. 204.1.

Syndrome of inappropriate ADH secretion

In some patients secretion of antidiuretic hormone (ADH; vasopressin) occurs despite hypotonicity of the extracellular fluid and normal or raised fluid volume, and such patients are said to have the syndrome of inappropriate ADH secretion (SIADH). With severe water excess, the resultant hyponatraemia may result in symptoms ranging from lassitude or headache to profound neurological symptoms such as confusion, convulsions, or coma. Some patients may experience inappropriate thirst as well as ADH secretion, thus exacerbating their condition. For a discussion of sodium homoeostasis and dilutional hyponatraemia, see p. 1777.3 and p. 1778.1.

Conditions that can precipitate SIADH include CNS disorders, infections such as encephalitis and meningitis, head trauma, porphyria, or pulmonary diseases such as tuberculosis and pneumonia. ADH may also be secreted ectopically from malignancies, most commonly from small-cell bronchial carcinoma. SIADH may also be drug-induced; drugs associated with the condition include carbamazepine, chlorpropamide, cytotoxic drugs such as cyclophosphamide and the vinca alkaloids, oxytocin, some antipsychotics, tricyclic antidepressants, and SSRIs.

Diagnosis of SIADH is initially prompted by the presence of hyponatraemia and corresponding plasma hypo-osmolality with or without neurological symptoms. Hypervolaemia, persistent excess sodium excretion, lack of oedema, and normality of both renal and adrenal function are confirmatory.

Mild water excess is frequently asymptomatic and may not require specific therapy, but patients with SIADH often have a more severe disorder and treatment is best aimed at the underlying cause. If such treatment is not possible or if symptoms persist, water restriction may be considered. However, fluid restriction is unpleasant, particularly for patients who retain inappropriate thirst, and may not be tolerable. In these patients demeclocycline may be given to antagonise the effect of ADH on the renal tubules. Lithium has been given as an alternative but has a high frequency of adverse effects, and phenytoin has been used occasionally to inhibit pituitary ADH secretion. Diuretics such as furosemide (used with oral sodium chloride) have been tried in an attempt to optimise diuresis while retaining sodium. Oral urea has also been used in a small number of patients. In patients with life-threatening severe acute water intoxication (see Hyponatraemia, p. 1778.1), treatment initially involves cautious improvement of the profound hyponatraemia by intravenous infusion of hypertonic (usually 3%) or isotonic sodium chloride, often with furosemide or another loop diuretic to avoid volume expansion. Drugs that act directly in the renal tubules as vasopressin V_2 receptor antagonists such as tolvaptan are also used.

References.
1. Kinzie BJ. Management of the syndrome of inappropriate secretion of antidiuretic hormone. *Clin Pharm* 1987; **6**: 625–33.
2. Kovacs L, Robertson GL. Syndrome of inappropriate antidiuresis. *Endocrinol Metab Clin North Am* 1992; **21**: 859–75.
3. Miller M. Syndromes of excess antidiuretic hormone release. *Crit Care Clin* 2001; **17**: 11–23.
4. Verbalis JG. Vasopressin V_2 receptor antagonists. *J Mol Endocrinol* 2002; **29**: 1–9.
5. Rabinstein AA. Vasopressin antagonism: potential impact on neurologic disease. *Clin Neuropharmacol* 2006; **29**: 87–93.
6. Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; **356**: 2064–72.
7. Huang EA, *et al.* Oral urea for the treatment of chronic syndrome of inappropriate antidiuresis in children. *J Pediatr* 2006; **148**: 128–31.
8. Zietse R, *et al.* Current and future treatment options in SIADH. *NDT Plus* 2009; **2** (suppl 3): iii12–iii19.

Urinary-tract infections

The treatment of urinary-tract infections is discussed on p. 213.1.

Acetildenafil

Hongdenafil.

5-[2-Ethoxy-5-[2-(4-ethylpiperazine-1-yl)-acetyl]phenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one.

$C_{25}H_{34}N_6O_3$=466.6

CAS — 831217-01-7.

Profile

Acetildenafil is an analogue of sildenafil (p. 2364.1) that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction. Other drugs related to sildenafil detected in similar products include:

- aildenafil
- dimethyl sildenafil thione (sulfoaildenafil)
- homosildenafil
- hydroxyhomosildenafil.
- nor-acetildenafil
- sulfohomosildenafil

Alfuzosin Hydrochloride

(BANM, USAN, rINNM)

Alfutsoslinihydrokloridi; Alfuzosin Hidroklorür; Alfuzosina, hidrocloruro de; Alfuzosine, Chlorhydrate d'; Alfuzosin-hydrochlorid; Alfuzosinhydrochlorid; Alfuzosinhydrokloridi; Alfuzosini Hydrochloridum; Alfuzozin-hidroklorid; Alfuzozino hidrochloridas; Hidrocloruro de alfuzosina; SL-77499-10; SL-77499 (alfuzosin); Альфузозина Гидрохлорид.

N-[3-[4-Amino-6,7-dimethoxyquinazolin-2-yl(methyl)amino] propyl]tetrahydro-2-furamide hydrochloride.

$C_{19}H_{27}N_5O_4HCl$=425.9

CAS — 81403-80-7 (alfuzosin); 81403-68-1 (alfuzosin hydrochloride).

ATC — G04CA01.

ATC Vet — QG04CA01.

UNII — 75046A1XTN.

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

Ph. Eur. 8: (Alfuzosin Hydrochloride). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Alfuzosin Hydrochloride). A white to almost white, slightly hygroscopic, powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

Uses and Administration

Alfuzosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions similar to those of prazosin (p. 1474.1). It acts preferentially on receptors in the lower urinary tract and is therefore used in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction, including acute urinary retention.

Alfuzosin is given orally as the hydrochloride. Like other alpha$_1$-adrenoceptor blockers, it may cause collapse in some patients after the first dose, which should therefore be given just before bedtime to reduce the risk. Doses may need to be reduced in patients with hepatic or renal impairment (see p. 2352.1); the initial dose should also be reduced in the elderly.

In **benign prostatic hyperplasia**, the usual dose of alfuzosin hydrochloride is 2.5 mg three times daily, increased to 10 mg daily if necessary. In elderly patients, and those receiving treatment for hypertension, a lower

initial dose of 2.5 mg twice daily should be considered. A modified-release preparation may also be used in a dose of 10 mg once daily after a meal.

In patients aged over 65 years catheterised for **acute urinary retention** associated with benign prostatic hyperplasia, a modified-release preparation may be given in a dose of 10 mg once daily after a meal for 3 to 4 days.

Reviews.

1. Wilde MI, *et al.* Alfuzosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in benign prostatic hyperplasia. *Drugs* 1993; 45: 410–29.
2. McKeage K, Plosker GL. Alfuzosin: a review of the therapeutic use of the prolonged-release formulation given once daily in the management of benign prostatic hyperplasia. *Drugs* 2002; 62: 633–53.
3. Lee M. Alfuzosin hydrochloride for the treatment of benign prostatic hyperplasia. *Am J Health-Syst Pharm* 2003; 60: 1426–39. Correction. *ibid.* 2004; 61: 437.
4. Weiner DM, Lowe FC. Alfuzosin for the management of benign prostate hyperplasia. *Expert Opin Pharmacother* 2003; 4: 2057–63.
5. Guay DR. Extended-release alfuzosin hydrochloride: a new alpha-adrenergic receptor antagonist for symptomatic benign prostatic hyperplasia. *Am J Geriatr Pharmacother* 2004; 2: 14–23.
6. MacDonald R, Wilt TJ. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. *Urology* 2005; 66: 780–8.
7. McVary KT. Alfuzosin for symptomatic benign prostatic hyperplasia: long-term experience. *J Urol (Baltimore)* 2006; 175: 35–42.
8. Roehrborn CG, Rosen RC. Medical therapy options for aging men with benign prostatic hyperplasia: focus on alfuzosin 10 mg once daily. *Clin Interv Aging* 2008; 3: 511–24.

Administration in hepatic or renal impairment. Alfuzosin should be avoided in patients with severe hepatic impairment; in those with mild to moderate impairment the initial oral dose of alfuzosin hydrochloride should be 2.5 mg daily, increased to 2.5 mg twice daily according to response.

The findings of a study[1] in 18 subjects with varying degrees of renal impairment (including 6 with severe impairment) given a single dose of alfuzosin 10 mg as a once-daily, modified-release formulation suggested that no dose reduction was needed in patients with impaired renal function. At most, slight pharmacokinetic modifications were found in those with renal impairment when compared with those with normal function. It should also be noted that the renal clearance of alfuzosin is a minor route of elimination (see Pharmacokinetics, below). Licensed product information recommends that patients with renal impairment are started on a dose of 2.5 mg twice daily, thereafter adjusted according to response.

1. Marbury TC, *et al.* Pharmacokinetics and safety of a single oral dose of once-daily alfuzosin, 10 mg, in male subjects with mild to severe renal impairment. *J Clin Pharmacol* 2002; 42: 1311–17.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3 and p. 1475.1. Alfuzosin may be more selective for the urinary tract and vasodilator effects may be less frequent. Additional adverse effects of alfuzosin include rhinitis, bronchitis, sinusitis, pharyngitis, and upper respiratory-tract infections. Angina has occurred in patients with pre-existing ischaemic heart disease; if symptoms appear or worsen during treatment, alfuzosin should be stopped. Prolongation of the QT interval has been reported during alfuzosin treatment, and it should be used with caution in patients with acquired or congenital QT prolongation, or those who are taking other drugs that prolong the QT interval. Hepatocellular and cholestatic liver injury, including jaundice, has occurred and may require treatment to be stopped. Alfuzosin should be avoided in severe hepatic impairment, and doses may need to be reduced in mild to moderate hepatic impairment and in renal impairment (see above).

Incidence of adverse effects. In postmarketing surveillance involving 13 389 patients given oral alfuzosin 2.5 mg three times daily for benign prostatic hyperplasia, about 3.7% of patients failed to complete treatment because of adverse effects. These were mostly vasodilator effects (vertigo or dizziness, syncope or malaise, hypotension, and headache), and were more common in patients over 75 years of age and during the first week of treatment.[1]

1. Lukacs B, *et al.* Safety profile of 3 months' therapy with alfuzosin in 13,389 patients suffering from benign prostatic hypertrophy. *Eur Urol* 1996; 29: 29–35.

Cataract surgery. Alpha blockers, including alfuzosin, have been associated with intraoperative floppy iris syndrome in cataract surgery patients. For further details, see under Tamsulosin, p. 2369.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alfuzosin 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

As for Prazosin Hydrochloride, p. 1475.1. Potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, itraconazole, and ritonavir, may increase blood concentrations of alfuzosin.

Pharmacokinetics

Alfuzosin is readily absorbed after oral doses and peak plasma concentrations generally occur 0.5 to 3 hours after a dose; bioavailability is about 64%. Absorption from modified-release preparations is improved if given with food. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, to inactive metabolites that are excreted primarily in faeces via the bile. Only about 11% of a dose is excreted unchanged in the urine. Alfuzosin has a plasma elimination half-life of 3 to 5 hours. It is 90% bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dalfaz; UroXatral; ***Austria***: Xatral; ***Belg.***: Xatral; ***Braz.***: Xatral; ***Canad.***: Xatral; ***Chile***: UroXatral; ***China***: Nuo Shu An (诺舒安); WeiPing (维平); Xatral (桑塔); *Cz.*: Alfuzostad; Xatral; ***Denm.***: Danafusin; Prostazosin; Xatral; ***Fin.***: Danafusin; Lafunomyl; Xatral; ***Fr.***: Urion; Xatral; ***Ger.***: Alfunar; Alfusin†; Urion†; UroXatral†; ***Gr.***: Alcinin; Alfuprost; Alfural; Alfuzin; Innosensitive; Ofuxal; Rilif; Spedamyl; Xatral; Zoprost; Zoratral; ***Hong Kong***: Xatral; ***Hung.***: Alfetim; Alfugen; Alfuzostad; Fetamozin; ***India***: Alfoo; Alfusin; Elzu; Flotral; Fual; ***Indon.***: Xatral; ***Irl.***: Alfirum†; Alfu; Alzmeran; Tevax; Xatger; Xatral; ***Israel***: Alfu-Kal; Xatral; ***Ital.***: Mittoval; Xatral; ***Malaysia***: Xatral; ***Mex.***: Ranplasia; Xatral; ***Neth.***: Xatral; ***Norw.***: Xatral†; ***Philipp.***: Fozal; Profuzosin; Xatral; ***Pol.***: AlfuLEK; Alfuzostad; Alugen; Dalfaz; ***Port.***: Benestan; ***Rus.***: Dalfaz (Дальфаз); ***S.Afr.***: Rantral; Xatral; ***Singapore***: Xatral; ***Spain***: Benestan; Unibenestan; ***Swed.***: Danafusin; Lafunomyl; Xatral; ***Switz.***: Fuzocim; Xatral; ***Thai.***: Xatral; ***Turk.***: Xatral; ***UK***: Besavar; Vasran; Xatral; ***Ukr.***: Dalfusin (Дальфузин)†; ***USA***: UroXatral; ***Venez.***: Xatral.

Multi-ingredient Preparations. ***Hung.***: Alfin Combo; ***India***: Alfura; Dutalfa; ***Mex.***: Profidox.

Pharmacopoeial Preparations

BP 2014: Alfuzosin Tablets; Prolonged-release Alfuzosin Tablets; **USP 36:** Alfuzosin Hydrochloride Extended-Release Tablets.

Alprostadil *(BAN, USAN, rINN)*

Alprostadilli; Alprostadilis; Alprostadilum; Alprosztadil; PGE_1; Prostaglandin E_1; U-10136; Алпростадил.

(E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxoprost-13-enoic acid; 7-{(1R,2R,3R)-3-Hydroxy-2-[(E)-(3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl}heptanoic acid.

$C_{20}H_{34}O_5$=354.5

CAS — 745-65-3.

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.

UNII — FSTD010360.

NOTE. In *Martindale* the term alprostadil is used for the exogenous substance and prostaglandin E_1 for the endogenous substance.

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

Ph. Eur. 8: (Alprostadil). A white or slightly yellowish crystalline powder. Practically insoluble in water; freely soluble in alcohol; soluble in acetone; slightly soluble in ethyl acetate.

USP 36: (Alprostadil). A white to off-white crystalline powder. M.p. about 110 degrees. Soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in chloroform and in ether; slightly soluble in ethyl acetate. Store between 2 degrees and 8 degrees in airtight containers.

Alprostadil Alfadex *(BAN, rINNM)*

Alprostadilum Alfadexum; α-Cyclodextrin Alprostadil; PGE_1 α-CD; Prostaglandin E_1 α-Cyclodextrin Clathrate Compound; Алпростадил Альфадекс.

$C_{20}H_{34}O_5.x(C_{36}H_{60}O_{30})$

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Alprostadil is a prostaglandin (p. 2598.1) that causes vasodilatation and prevents platelet aggregation. The endogenous substance is termed prostaglandin E_1. Alprostadil is used mainly in congenital heart disease and in erectile dysfunction (p. 2348.2).

In the management of **erectile dysfunction,** alprostadil is given by intracavernosal injection; preparations may contain alprostadil or alprostadil alfadex, but the dose is expressed in terms of the base. Alprostadil may also be given as an intra-urethral application.

By *intracavernosal injection*, the initial dose should be low, for example 2.5 micrograms, and is increased incrementally until a suitable dose is established. Normally, the second dose should be 5 micrograms if some response to the first dose is seen, or 7.5 micrograms if there is no response; increments should then be of 5 to 10 micrograms until an effective dose is reached. The usual dose range is 5 to 20 micrograms and the maximum recommended dose is 60 micrograms. In cases of erectile dysfunction of neurogenic origin secondary to spinal cord injury an initial dose of 1.25 micrograms has been given, with a second dose of 2.5 micrograms, a third dose of 5 micrograms, and subsequent increments of 5 micrograms. While finding a suitable dose, the interval between doses should be at least 1 day if there has been a partial response. If there is no response however, the next, higher dose may be given within 1 hour. Once established, the optimal dose should be given not more than once daily and not more than three times per week.

Alprostadil may also be injected intracavernosally in the diagnosis of erectile dysfunction in doses ranging from 5 to 20 micrograms.

By *intra-urethral (transurethral) application*, the initial dose is 250 micrograms. The dose may be increased incrementally to 500 or 1000 micrograms or decreased to 125 micrograms according to response. The optimal dose should be given not more than twice daily, and not more than seven times per week. A dose of 500 micrograms may be used diagnostically.

Alprostadil is also available in some countries as a *topical* formulation for the treatment of erectile dysfunction. There is also ongoing investigation of the use of topical formulations for female sexual dysfunction. An injectable liposomal formulation of alprostadil (lipo-prostaglandin E_1, lipo-PGE_1) has also been investigated for various uses.

For doses used in neonates with **congenital heart disease** to maintain the patency of the ductus arteriosus, see Administration in Children, below.

Administration in children. Alprostadil is used to maintain the patency of the ductus arteriosus in neonates with congenital heart disease until surgery is possible. It is given by continuous intravenous infusion beginning with doses of 50 to 100 nanograms/kg per minute; doses should be reduced as soon as possible to the minimum necessary to maintain response. Lower starting doses may be effective in some patients, and UK licensed product information advises that doses as low as 5 nanograms/kg per minute have been used successfully when transport of the infant is necessary. The *BNFC* suggests an initial dose of 5 nanograms/kg per minute, adjusted in steps of 5 nanograms/kg per minute according to response, to a maximum of 100 nanograms/kg per minute. The dose can be increased to 400 nanograms/kg per minute according to US licensed product information but, in general, higher infusion rates do not improve effect. Alprostadil may also be given by continuous infusion through an umbilical artery catheter placed at the ductal opening.

Ergotamine poisoning. Alprostadil[1,2] is one of many drugs that have been used to treat the circulatory disturbances in ergotamine poisoning (see Cardiovascular Effects, p. 674.3).

1. Levy JM, *et al.* Prostaglandin E_1 for alleviating symptoms of ergot intoxication: a case report. *Cardiovasc Interv Radiol* 1984; 7: 28–30.
2. Horstmann R, *et al.* Kritische Extremitätenischämie durch Ergotismus. *Dtsch Med Wochenschr* 1993; 118: 1067–71.

Haemorrhagic cystitis. Bladder irrigation with alprostadil produced resolution of severe haemorrhagic cystitis in 5 of 6 children who had undergone bone marrow transplantation.[1] Alprostadil was given via a catheter and retained for 1 hour each day for at least 7 consecutive days.

1. Trigg ME, *et al.* Prostaglandin E_1 bladder instillations to control severe hemorrhagic cystitis. *J Urol (Baltimore)* 1990; 143: 92–4.

Hearing loss. Alprostadil has been used in the treatment of sudden hearing loss to increase cochlear blood flow and oxygen supply. Results of a meta-analysis of 13 randomised studies suggested that those patients treated with alprostadil had an improvement in their hearing when compared with controls.[1]

1. Zhuo X-L, *et al.* Is the application of prostaglandin E_1 effective for the treatment of sudden hearing loss? An evidence-based meta-analysis. *J Int Med Res* 2008; 36: 467–70.

Hepatic disorders. Benefit has been reported in patients with *viral hepatitis* (p. 952.1) given intravenous alprostadil alone or followed by oral dinoprostone or misoprostol.[1,2] Prostaglandins were studied because they had previously been shown to have a cytoprotective effect in experimentally induced hepatitis or in isolated hepatocytes, but the

mechanism by which they exerted a beneficial effect was uncertain.

Combined intravenous therapy with glucagon, insulin, and alprostadil formulated in lipid microspheres has also been found effective in preventing *acute fulminant hepatic failure* after hepatic arterial infusion of antineoplastic chemotherapy.[3]

1. Sinclair SB, *et al.* Biochemical and clinical response of fulminant viral hepatitis to administration of prostaglandin E: a preliminary report. *J Clin Invest* 1989; 84: 1063–9.
2. Flowers M, *et al.* Prostaglandin E in the treatment of recurrent hepatitis B infection after orthotopic liver transplantation. *Transplantation* 1994; 58: 183–92.
3. Ikegami T, *et al.* Randomized control trial of lipo-prostaglandin E_1 in patients with acute liver injury induced by Lipiodol-targeted chemotherapy. *Clin Pharmacol Ther* 1995; 57: 582–9.

Organ and tissue transplantation. Alprostadil and other prostaglandin analogues have been investigated in regimens for the management of solid organ transplantation, with variable results. For reference to the use of alprostadil in intestinal grafts see p. 1935.1.

References.

1. Merion RM. Prostaglandins in liver transplantation. *Adv Exp Med Biol* 1997; 433: 13–18.
2. Iberer F, *et al.* Prostaglandins in heart transplantation. *Adv Exp Med Biol* 1997; 433: 19–22.
3. Ray JG. Prostaglandin E1 analogs do not improve renal function among either transplant or nontransplant patients: no further trials required. *Transplantation* 1998; 66: 476–83.

Peripheral vascular disease. Various prostaglandins, including alprostadil,[1-7] have been used 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.

1. Clifford PC, *et al.* Treatment of vasospastic disease with prostaglandin E_1. *BMJ* 1980; 281: 1031–4.
2. Telles GS, *et al.* Prostaglandin E_1 in severe lower limb ischaemia: a double-blind controlled trial. *Br J Surg* 1984; 71: 506–8.
3. Mohrland JS, *et al.* A multiclinic, placebo-controlled, double-blind study of prostaglandin E_1 in Raynaud's syndrome. *Ann Rheum Dis* 1985; 44: 754–60.
4. Sethi GK, *et al.* Intravenous infusion of prostaglandin E_1 (PGE_1) in management of limb ischemia. *Ann Surg* 1986; 52: 474–8.
5. Langevitz P, *et al.* Treatment of refractory ischemic skin ulcers in patients with Raynaud's phenomenon with PGE_1 infusions. *J Rheumatol* 1989; 16: 1433–5.
6. The ICAI Study Group. Prostanoids for chronic critical leg ischemia: a randomized, controlled, open-label trial with prostaglandin E_1. *Ann Intern Med* 1999; 130: 412–21.
7. Bartolone S, *et al.* Efficacy evaluation of prostaglandin E1 against placebo in patients with progressive systemic sclerosis and significant Raynaud's phenomenon. *Minerva Cardioangiol* 1999; 47: 137–43.

Pulmonary hypertension. Alprostadil has shown some beneficial effects in patients with pulmonary arterial hypertension.[1,2]

1. Shen J, *et al.* Effects of lipo-prostaglandin E1 on pulmonary hemodynamics and clinical outcomes in patients with pulmonary arterial hypertension. *Chest* 2005; 128: 714–19.
2. von Scheidt W, *et al.* Prostaglandin E1 testing in heart failure-associated pulmonary hypertension enables transplantation: the PROPHET study. *J Heart Lung Transplant* 2006; 25: 1070–6.

Adverse Effects, Treatment, and Precautions

The adverse effects reported most commonly in **infants** with congenital heart disease treated with alprostadil are apnoea, fever, flushing, hypotension, bradycardia, tachycardia, diarrhoea, and convulsions. Other adverse effects reported include oedema, cardiac arrest, hypokalaemia, disseminated intravascular coagulation, and cortical proliferation of the long bones. Weakening of the wall of the ductus arteriosus and pulmonary artery may occur on prolonged infusion. Alprostadil should be avoided in neonates with respiratory distress syndrome and should be used with caution in those with bleeding tendencies; blood pressure and respiratory status should be monitored during infusion.

Adverse effects reported in **adults** given alprostadil have included headache, flushing, hypotension, diarrhoea, and pain and inflammation at the infusion site.

After intracavernosal or intra-urethral alprostadil for the treatment of erectile dysfunction, the most frequently reported adverse effect is pain during erection. Local reactions including penile fibrosis, fibrotic nodules, and Peyronie's disease have been reported. Priapism may occur (see below). Systemic effects are less common but hypotension and other adverse effects have been reported. Intracavernosal or intra-urethral use should be avoided in patients with complicating penile deformities or with sickle-cell disease, myeloma, leukaemias, or other conditions predisposing to prolonged erection.

In children. Reviews[1,2] of adverse effects associated with alprostadil in infants with congenital heart disease.

1. Lewis AB, *et al.* Side effects of therapy with prostaglandin E_1 in infants with critical congenital heart disease. *Circulation* 1981; 64: 893–8.
2. Lucron H, *et al.* Complications du traitement par prostaglandines E1 des cardiopathies congénitales en réanimation médicale pédiatrique. *Arch Mal Coeur Vaiss* 2005; 98: 524–30.

Effects on the bones. Periosteal or cortical hyperostosis has been reported in infants given alprostadil for cyanotic congenital heart disease.[1,2] A retrospective review of 30 infants[3] treated with alprostadil revealed radiographic signs of periosteal reactions in 5. Changes could be detected after even short courses of therapy; 3 developed relatively mild periosteal changes in the ribs after infusions ranging from 9 to 205 hours and one had involvement of the left femur after infusion for 71 hours. Resolution of lesions had occurred in most bones 6 to 12 months later. In a further study,[4] radiological evidence of cortical hyperostosis was found in 53 of 86 infant heart transplant recipients who had received alprostadil infusion pre-operatively. Of 53 of the infants who had received alprostadil for less than 30 days, 21 were affected (2 severely). Correspondingly, of those treated for 30 to 60 days, 18 of 22 were affected (13 severely). All 14 infants treated for more than 60 days were affected (7 severely). Since the associated bone changes may persist for months after stopping alprostadil, caution should be exercised to avoid misdiagnosis.

1. Kalloghlian AK, *et al.* Cortical hyperostosis simulating osteomyelitis after short-term prostaglandin E_1 infusion. *Eur J Pediatr* 1996; 155: 173–4.
2. Estes K, *et al.* Cortical hyperostosis secondary to prostaglandin E_1 therapy. *J Pediatr* 2007; 151: 441.
3. Ringel RE, *et al.* Periosteal changes secondary to prostaglandin administration. *J Pediatr* 1983; 103: 251–3.
4. Woo K, *et al.* Cortical hyperostosis: a complication of prolonged prostaglandin infusion in infants awaiting cardiac transplantation. *Pediatrics* 1994; 93: 417–20.

Effects on the gastrointestinal tract. Hyperplasia of the gastric mucosa, resulting in gastric outlet obstruction, has been reported in several neonates receiving alprostadil infusion.[1-3] It was suggested that this effect was dose-dependent.[1] Regression of the obstruction usually occurred after cessation of therapy.

For a report of necrotising enterocolitis in infants receiving alprostadil for congenital heart disease, see Dinoprostone, p. 2135.2.

1. Peled N, *et al.* Gastric-outlet obstruction induced by prostaglandin therapy in neonates. *N Engl J Med* 1992; 327: 505–10.
2. Merkus PJFM, *et al.* Prostaglandin E1 and gastric outlet obstruction in infants. *Lancet* 1993; 342: 747.
3. Kobayashi N, *et al.* Acute gastric outlet obstruction following the administration of prostaglandin: an additional case. *Pediatr Radiol* 1997; 27: 57–9.

Effects on the metabolism. Severe hyperglycaemia with apparent ketoacidosis occurred during postoperative infusion of alprostadil in the infant of a diabetic mother.[1] The manufacturers had received reports of hyperglycaemia associated with alprostadil in 5 infants, one of whom had a diabetic mother. Hypoglycaemia has also been reported in a few infants.[2]

1. Cohen MH, Nihill MR. Postoperative ketotic hyperglycaemia during prostaglandin E_1 infusion in infancy. *Pediatrics* 1983; 71: 842–4.
2. Lewis AB, *et al.* Side effects of therapy with prostaglandin E_1 in infants with critical congenital heart disease. *Circulation* 1981; 64: 893–8.

Effects on the skin. A 63-year-old man with Peyronie's disease[1] developed toxic pustuloderma (acute generalised exanthematous pustulosis) 6 days after receiving a single intracavernosal injection of alprostadil to define the penile morphology. He was treated with antihistamines and topical corticosteroids and the condition resolved completely within a week.

1. Gallego L, *et al.* Toxic pustuloderma induced by intracavernous prostaglandin E_1. *Br J Dermatol* 1997; 136: 975–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alprostadil 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)

Priapism. If priapism (p. 1430.2) occurs after the use of alprostadil for erectile dysfunction, its treatment should not be delayed more than 6 hours. The *BNF* recommends initial therapy by penile aspiration. If aspiration is unsuccessful sodium chloride 0.9% can be injected into one side of the corpus cavernosum and drained through the other side. If both aspiration and lavage have been unsuccessful, a sympathomimetic with action on alpha-adrenergic receptors is given by cautious intracavernosal injection, with continuous monitoring of blood pressure and pulse. Extreme caution is necessary in patients with coronary heart disease, hypertension, cerebral ischaemia, or if taking an antidepressant. Low doses and dilute solutions are recommended as follows:

- intracavernosal injection of phenylephrine 100 to 200 micrograms (0.5 to 1 mL of a 200 micrograms/mL solution) every 5 to 10 minutes; maximum total dose 1 mg

alternatively

- intracavernosal injection of adrenaline 10 to 20 micrograms (0.5 to 1 mL of a 20 micrograms/mL solution) every 5 to 10 minutes; maximum total dose 100 micrograms

alternatively

- intracavernosal injection of metaraminol may be used, but it should be noted that fatal hypertensive crises have been reported; metaraminol 100 micrograms (5 mL of a 20 micrograms/mL solution) may be given by careful slow injection every 15 minutes; a maximum total dose of up to 1 mg has been suggested

If necessary the sympathomimetic injections can be followed by further penile aspiration. If sympathomimetics are unsuccessful, urgent surgical referral is required.

Pharmacokinetics

On infusion alprostadil is rapidly metabolised by oxidation during passage through the pulmonary circulation. It is excreted in the urine as metabolites within about 24 hours. Systemic absorption of alprostadil occurs after intracavernosal injection.

References.

1. Cox JW, *et al.* Pulmonary extraction and pharmacokinetics of prostaglandin E_1 during continuous intravenous infusion in patients with adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 137: 5–12.
2. Cawello W, *et al.* Dose proportional pharmacokinetics of alprostadil (prostaglandin E_1) in healthy volunteers following intravenous infusion. *Br J Clin Pharmacol* 1995; 40: 273–6.
3. Lea AP, *et al.* Intracavernous alprostadil: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in erectile dysfunction. *Drugs Aging* 1996; 8: 56–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cardiobron; Prolisina VR; Prostavasin; ***Austral.***: Caverject; Prostin VR; ***Austria***: Alprostapint; Caverject; Minprog; Pridax; Prostavasin; ***Belg.***: Caverject; Prostin VR; ***Braz.***: Aplicav; Caverject; Prostavasin; ***Canad.***: Caverject; Muse; Prostin VR; ***Chile***: Caverject; Prostin Pediatrico; ***China***: Bi Fa Er (比法尔); Bolesi (勃乐斯); Kai Tong (凯彤); Kaishi (凯时); Prostavasin (保达新); Ruitong (锐通); Yu Ge (誉歌); *Cz.*: Alprestil; Alprostan; Alprostapint; Caverject†; Karon; Muse†; Prostavasin; ***Denm.***: Caverject; Muse; Prostivas; ***Fin.***: Caverject; Muse; Prostivas; ***Fr.***: Caverject; Caverjectdual; Edex; Muse; Prostine VR; ***Ger.***: Caverject; Minprog; Muse; Pridax; Prostavasin; Viridal; ***Gr.***: Caverject; Edex; Muse; Prostavasin; Prostin VR; ***Hong Kong***: Befar; Caverject; Eglandin†; Prostavasin†; Prostin VR; ***Hung.***: Alprestil; Alprostapint†; Caverject; Prostavasin; Prostin VR; ***India***: Alpostin; Bioglandin; Prostin VR; ***Irl.***: Caverject; Muse; Viridal; ***Israel***: Alprostapint†; Caverject; Prostin VR; ***Ital.***: Alprostar; Caverject; Muse; Prostavasin; Prostin VR; Viridal†; ***Jpn***: Liple; Palux; Prostandin; ***Malaysia***: Caverject; Prostin VR; ***Mex.***: Caverject; ***Neth.***: Muse; Prostin VR; ***Norw.***: Bondil; Caverject; Prostivas; ***NZ***: Caverject; Prostin VR; ***Pol.***: Caverject†; Prostavasin; Prostin VR; ***Port.***: Caverject; Muse; Prostin VR; Vasoprost; ***Rus.***: Alprostan (Алпростан); Caverject (Каверджект); Prostin VR (Простин ВР); Vasaprostan (Вазапростан); ***S.Afr.***: Caverject; Muse†; Prostin VR; ***Singapore***: Caverject; Prostin VR; ***Spain***: Caverject; Muse; Sugiran; ***Swed.***: Bondil; Caverject; Prostivas; ***Switz.***: Caverject; Muse; Prostin VR; ***Thai.***: Prostin VR; ***UK***: Caverject; Muse; Prostin VR; Viridal; ***Ukr.***: Vazaprostan (Вазапростан); ***USA***: Caverject; Edex; Muse; Prostin VR; ***Venez.***: Caverject.

Multi-ingredient Preparations. *USA*: Tri-Mix.

Pharmacopoeial Preparations
USP 36: Alprostadil Injection.

Aminotadalafil

Аминотадалафил.
6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-aminopyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione.
$C_{21}H_{18}N_4O_4$=390.4
UNII — FY501QO030.

Profile

Aminotadalafil is an analogue of tadalafil (p. 2368.1) that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction.

Avanafil *(USAN, rINN)*

Avanafilo; Avanafilum; TA-1790; Аванафил.
4-[(3-Chloro-4-methoxybenzyl)amino]-2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]-*N*-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide.
$C_{23}H_{26}ClN_7O_3$=484.0
CAS — 330784-47-9.
UNII — DR5S136IVO.

The symbol † denotes a preparation no longer actively marketed

Uses and Administration

Avanafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2). It is used orally in the management of erectile dysfunction (p. 2348.2). The usual dose is 100 mg taken about 30 minutes before sexual intercourse. The dose may be increased to 200 mg, or decreased to 50 mg, depending on response. Avanafil should not be taken more than once in 24 hours.

In patients stabilised on alpha blocker therapy, the initial dose of avanafil should be no more than 50 mg daily. A maximum dose of 50 mg daily is also advised in patients taking avanafil with moderate inhibitors of cytochrome P450 isoenzyme CYP3A4.

References.
1. Limin M, *et al.* Avanafil, a new rapid-onset phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction. *Expert Opin Invest Drugs* 2010; 19: 1427–37.
2. Alwaal A, *et al.* Future prospects in the treatment of erectile dysfunction: focus on avanafil. *Drug Des Devel Ther* 2011; 5: 435–43.
3. Goldstein I, *et al.* A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. *J Sex Med* 2012; 9: 1122–33.
4. Segal R, Burnett AL. Avanafil for the treatment of erectile dysfunction. *Drugs Today* 2012; 48: 7–15.
5. Zhao C, *et al.* Efficacy and safety of avanafil for treating erectile dysfunction: results of a multicentre, randomized, double-blind, placebo-controlled trial. *BJU Int* 2012. Available at: doi:10.1111/j.1464-410X.2012.11095.x

Adverse Effects and Precautions

As for Sildenafil, p. 2365.2 and p. 2366.2. The use of avanafil is not recommended in patients with severe hepatic or renal impairment or in dialysis patients; however, this is due to a lack of data and no dosage adjustment is needed in mild or moderate hepatic (Child-Pugh class A or B) or renal (creatinine clearance of 30 to less than 90 mL/min) impairment.

Interactions

As for Sildenafil, p. 2366.3. Avanafil should not be given with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4. When given with moderate CYP3A4 inhibitors, dosage of avanafil must be reduced and suggested doses are given below (above). An enhanced hypotensive effect may be seen if avanafil is taken with substantial amounts of alcohol.

Pharmacokinetics

Avanafil is rapidly absorbed after an oral dose. Peak plasma concentrations occur within a median of 30 to 45 minutes; the rate of absorption is reduced when avanafil is given with a high-fat meal although this is considered to have minimal clinical significance. It is about 99% bound to plasma proteins.

Avanafil is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP3A4 and to a minor extent by the CYP2C isoform. Two major metabolites are produced, one of which is active. Avanafil is excreted as metabolites mainly in the faeces (about 62%), and to a lesser extent in the urine (about 21%). The terminal elimination half-life is about 5 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Stendra.

Benzamidenafil

N-((3,4-dimethoxyphenyl)methyl)-2-(1-hydroxypropan-2-ylamino)-5-nitro-benzamide.
$C_{19}H_{23}N_3O_6$=389.4
CAS — 1020251-53-9.

Profile

Benzamidenafil is a phosphodiesterase type-5 inhibitor that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction.

References.
1. Zou P, *et al.* Identification of benzamidenafil, a new class of phosphodiesterase-5 inhibitor, as an adulterant in a dietary supplement. *J Pharm Biomed Anal* 2008; 47: 255–9.

Dapoxetine *(rINN)*

Dapoxetina; Dapoxétine; Dapoxetinum; LY-210448; Дапоксетин.
(+)-(S)-*N*,*N*-Dimethyl-α-[2-(1-naphthyloxy)ethyl]benzylamine.
$C_{21}H_{23}NO$=305.4
CAS — 119356-77-3.
ATC — G04BX14.
ATC Vet — QG04BX14.
UNII — GB2433A4M3.

Dapoxetine Hydrochloride *(USAN, rINNM)*

Dapoxétine, Chlorhydrate de; Dapoxetini Hydrochloridum; Hidrocloruro de dapoxetina; Дапоксетина Гидрохлорид.
(+)-(S)-*N*, *N*-Dimethyl-alpha-[2-(1-naphthyloxy)ethyl]benzylamine hydrochloride.
$C_{21}H_{23}NO$, HCl=341.9
CAS — 129938-20-1.
ATC — G04BX14.
ATC Vet — QG04BX14.
UNII — U4OHT63MRI.

Profile

Dapoxetine is a rapidly absorbed short-acting SSRI used for on-demand treatment of premature ejaculation (p. 2350.2). Dapoxetine is usually given as the hydrochloride, but doses are expressed in terms of the base. A usual oral dose equivalent to dapoxetine 30 or 60 mg is taken 1 to 3 hours before sexual intercourse; this dose should not be taken more than once in 24 hours. Caution is required if the higher dose is given to patients who are taking potent cytochrome P450 isoenzyme CYP2D6 inhibitors or who are slow CYP2D6 metabolisers. A maximum dose of dapoxetine 30 mg is recommended for those taking moderate CYP3A4 inhibitors; dapoxetine is contra-indicated in patients taking potent CYP3A4 inhibitors.

Dapoxetine has been used to adulterate dietary supplements promoted for sexual health.

References.
1. Pryor JL, *et al.* Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. *Lancet* 2006; 368: 929–37.
2. Modi NB, *et al.* Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. *J Clin Pharmacol* 2006; 46: 301–9.
3. Andersson KE, *et al.* Pharmacokinetic and pharmacodynamic features of dapoxetine, a novel drug for 'on-demand' treatment of premature ejaculation. *BJU Int* 2006; 97: 311–15.
4. Dresser MJ, *et al.* Pharmacokinetics of dapoxetine, a new treatment for premature ejaculation: impact of age and effects of a high-fat meal. *J Clin Pharmacol* 2006; 46: 1023–9.
5. Shabsigh R, *et al.* Perceived control over ejaculation is central to treatment benefit in men with premature ejaculation: results from phase III trials with dapoxetine. *BJU Int* 2008; 102: 824–8.
6. Kaufman JM, *et al.* Treatment benefit of dapoxetine for premature ejaculation: results from a placebo-controlled phase III trial. *BJU Int* 2009; 103: 651–8.
7. Buvat J, *et al.* Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries. *Eur Urol* 2009; 55: 957–67.
8. Hellstrom WJG. Emerging treatments for premature ejaculation: focus on dapoxetine. *Neuropsychiatr Dis Treat* 2009; 5: 37–46.
9. McMahon C, *et al.* Dapoxetine 3003 Study Investigators. Treatment of premature ejaculation in the Asia-Pacific region: results from a phase III double-blind, parallel-group study of dapoxetine. *J Sex Med* 2010; 7: 256–68.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Extensil; *Austria*: Priligy; *Fin.*: Priligy; *Ger.*: Priligy; *Irl.*: Priligy; *Ital.*: Priligy; *Malaysia*: Priligy; *Neth.*: Priligy; *NZ*: Priligy; *Port.*: Priligy; *Singapore*: Priligy; *Spain*: Priligy; *Swed.*: Priligy; *UK*: Priligy.

Darifenacin *(BAN, USAN, rINN)*

Darifenacina; Darifénacine; Darifenacinum; UK-88525; Дарифенацин.
(*S*)-1-[2-(2,3-Dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-3-pyrrolidineacetamide.
$C_{28}H_{30}N_2O_2$=426.6
CAS — 133099-04-4.
ATC — G04BD10.
ATC Vet — QG04BD10.
UNII — APG9819VLM.

Darifenacin Hydrobromide *(BANM, USAN, rINNM)*

Darifénacine, Bromhydrate de; Darifenacini Hydrobromidum; Hidrobromuro de darifenacina; UK-88525-04; Дарифенацина Гидробромид.
(*S*)-2-[1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide hydrobromide.
$C_{28}H_{30}N_2O_2$,HBr=507.5
CAS — 133099-07-7.
ATC — G04BD10.
ATC Vet — QG04BD10.
UNII — CR02EYQ8GV.

Uses and Administration

Darifenacin is a selective M_3 antimuscarinic with actions similar to those of atropine (p. 1310.3); it is claimed to have a greater selectivity for the muscarinic receptors of the bladder.

Darifenacin is used in the management of urinary frequency, urgency, and incontinence in detrusor instability (p. 2349.2). It is given orally as the hydrobromide but doses are described in terms of the base: darifenacin hydrobromide 8.9 mg is equivalent to about 7.5 mg of darifenacin. The usual initial dose is the equivalent of darifenacin 7.5 mg once daily; after 2 weeks of treatment this may be increased to 15 mg once daily if necessary.

The starting dose of 7.5 mg should only be increased with caution in patients also receiving potent inhibitors of the cytochrome P450 isoenzyme CYP2D6, such as paroxetine and terbinafine. Darifenacin should be avoided, or a dose of 7.5 mg daily not exceeded, in patients also receiving potent inhibitors of CYP3A4, such as HIV-protease inhibitors, ketoconazole, and itraconazole. The dose of darifenacin should be increased with caution in the presence of moderate inhibitors of CYP3A4, such as macrolide antibacterials, fluconazole, and grapefruit juice.

Darifenacin should be used with caution in hepatic impairment, see below.

Darifenacin is being studied in irritable bowel syndrome.

References.
1. Haab F, *et al.* Darifenacin, an M_3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *Eur Urol* 2004; 45: 420–9.
2. Chapple C, *et al.* A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M_3 selective receptor antagonist, in the treatment of overactive bladder. *BJU Int* 2005; 95: 993–1001.
3. Foote J, *et al.* Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M_3 selective receptor antagonist. *Eur Urol* 2005; 48: 471–7.
4. Parsons M, *et al.* Darifenacin in the treatment of overactive bladder. *Int J Clin Pract* 2005; 59: 831–8.
5. Hill S, *et al.* Long-term darifenacin treatment for overactive bladder in patients aged 65 years and older: analysis of results from a 2-year, open-label extension study. *Curr Med Res Opin* 2007; 23: 2697–2704.
6. Dwyer P, *et al.* Long-term benefits of darifenacin treatment for patient quality of life: results from a 2-year extension study. *Neurourol Urodyn* 2008; 27: 540–7.

Administration in hepatic impairment. Licensed product information states that the oral dose of darifenacin should not exceed 7.5 mg once daily in patients with moderate hepatic impairment (Child-Pugh category B), and its use should be avoided in severe impairment (Child-Pugh category C).

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Darifenacin should be used with caution in patients also receiving inhibitors of cytochrome P450 isoenzymes (see Interactions, below and Uses and Administration, above). It should also be used with caution in hepatic impairment (see Administration in Hepatic Impairment, above).

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Exposure to darifenacin may be increased by drugs that inhibit the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Inducers of CYP3A4 may reduce plasma concentrations of darifenacin. Dosage adjustment for darifenacin may be necessary (see Uses and Administration, above). Darifenacin itself is also a moderate inhibitor of CYP2D6.

Pharmacokinetics

After an oral dose, darifenacin is subject to extensive first-pass metabolism and has a bioavailability of about 15 to 19%. It is about 98% bound to plasma proteins. Darifenacin is metabolised in the liver by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. The pharmacokinetics of darifenacin at steady state are dose-dependent because of the saturation of CYP2D6 metabolism. Most of a dose is excreted as metabolites in the urine and faeces.

References.
1. Kerbusch T, *et al.* Population pharmacokinetic modelling of darifenacin and its hydroxylated metabolite using pooled data, incorporating saturable first-pass metabolism, CYP2D6 genotype and formulation-dependent bioavailability. *Br J Clin Pharmacol* 2003; 56: 639–52.
2. Devineni D, *et al.* Pharmacokinetics of darifenacin, an M_3 selective receptor antagonist: effects of renal or hepatic impairment. *Br J Clin Pharmacol* 2005; 59: 632–3.
3. Skerjanec A. The clinical pharmacokinetics of darifenacin. *Clin Pharmacokinet* 2006; 45: 325–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Continex; Darisec; Enablex; Extracta†; *Austral.*: Enablex; *Belg.*: Emselex; *Braz.*: Enablex; *Canad.*: Enablex; *Cz.*: Emselex; *Denm.*: Emselex; *Ger.*: Emselex;

Gr.: Emselex; *Hung.*: Emselex; *India*: Dariten-OD; *Irl.*: Emselex; *Neth.*: Emselex; *Norw.*: Emselex; *Pol.*: Emselex; *Port.*: Emselex; *Rus.*: Enablex (Энаблекс); *S.Afr.*: Enablex; *Swed.*: Emselex; *Switz.*: Emselex; *Turk.*: Emselex; *UK*: Emselex; *USA*: Enablex.

Desmopressin *(BAN, rINN)* ⊗

DDAVP; Desmopresina; Desmopresinas; Desmopressiini; Desmopressine; Desmopressinum; Dezmopresszin; Десмопрессин.

1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin; [1-Deamino,8-D-arginine]vasopressin.

$C_{46}H_{64}N_{14}O_{12}S_2$=1069.2

CAS — 16679-58-6.

ATC — H01BA02.

ATC Vet — QH01BA02.

UNII — ENR1LLB0FP.

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

Ph. Eur. 8: (Desmopressin). A synthetic cyclic nonapeptide, available as an acetate. A white or almost white, fluffy powder. Soluble in water, in alcohol, and in glacial acetic acid. Store in airtight containers at 2 degrees to 8 degrees. Protect from light.

Desmopressin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de desmopresina; Desmopresin Asetat; Desmopresina, acetato de; Desmopressine, Acétate de; Desmopressini Acetas; Десмопрессина Ацетат.

$C_{46}H_{64}N_{14}O_{12}S_2.C_2H_4O_2.3H_2O$=1183.3

CAS — 62288-83-9 (anhydrous desmopressin acetate); 62357-86-2 (desmopressin acetate trihydrate).

ATC — H01BA02.

ATC Vet — QH01BA02.

UNII — XB13HYU18U.

Pharmacopoeias. In *US.*

USP 36: (Desmopressin Acetate). A white, fluffy powder. Soluble in water, in alcohol, and in acetic acid. Store in airtight containers at a temperature not exceeding 25 degrees, but preferably between 2 degrees and 8 degrees. Protect from light.

Units

27 units of desmopressin are contained in about 27 micrograms of desmopressin (with 5 mg of human albumin and citric acid) in one ampoule of the first International Standard (1980).

Uses and Administration

Desmopressin is a synthetic analogue of vasopressin (p. 2642.3). It has greater antidiuretic activity and a more prolonged action than vasopressin or lypressin. It also stimulates factor VIII and plasminogen activator activity in the blood, but has little pressor activity.

Desmopressin is used in the diagnosis and treatment of cranial diabetes insipidus, in the treatment of nocturnal enuresis, in tests of renal function, and for post-dural puncture headache. It is also used in the management of mild or moderate haemophilia and type I von Willebrand's disease, and in tests of fibrinolytic response.

It is given as the acetate, orally, as a solution intranasally, and by injection. The intranasal dose is about ten times that required intravenously and the oral dose about ten times greater than the intranasal dose. Doses are usually expressed in terms of desmopressin acetate, but for some preparations they are given in terms of the base; 110.7 micrograms of desmopressin acetate is equivalent to about 100 micrograms of desmopressin.

In the control of **cranial diabetes insipidus**, desmopressin acetate is given orally in usual initial doses of 100 micrograms three times daily. Doses may be adjusted according to response, with maintenance doses usually between 100 and 200 micrograms three times daily though total doses of between 100 micrograms and 1200 micrograms daily have been used.

A sublingual lyophilisate preparation containing desmopressin acetate is also available in the UK, but doses are expressed in terms of the base. The initial dose is equivalent to 60 micrograms of desmopressin given sublingually three times daily. The dose may be adjusted, with usual maintenance doses between 60 and 120 micrograms three times daily, though total doses of up to 720 micrograms daily have been used.

Desmopressin acetate may also be used intranasally in usual doses of 10 to 40 micrograms daily as a single dose or in divided doses.

It may also be given subcutaneously, intramuscularly, or intravenously in a dose of 1 to 4 micrograms daily.

A single intranasal dose of 20 micrograms or 2 micrograms subcutaneously or intramuscularly has been given in the **diagnosis** of diabetes insipidus.

In the **testing of renal function**, desmopressin acetate has been given intranasally in single doses of 40 micrograms and subcutaneously or intramuscularly in doses of 2 micrograms.

For **post-dural puncture headache**, a dose of desmopressin acetate 4 micrograms may be given by subcutaneous or intramuscular injection, either immediately before lumbar puncture or when headache occurs, and repeated after 24 hours if necessary (but see also p. 2356.2).

In the management of **primary nocturnal enuresis**, desmopressin acetate is given at bedtime in usual oral doses of 200 to 400 micrograms. The sublingual lyophilisate preparation may be given in a dose equivalent to desmopressin 120 micrograms, increasing to 240 micrograms if needed. The need for continued treatment should be reassessed after 3 months by withdrawing desmopressin for at least 1 week. For the view that nasal preparations should not be used for primary nocturnal enuresis, see Effects on Electrolytes, under Adverse Effects, p. 2356.3. For the control of **nocturia** in multiple sclerosis desmopressin acetate 10 to 20 micrograms intranasally at bedtime is recommended (but see Urinary Incontinence, p. 2356.2).

Desmopressin acetate is used to boost concentrations of factor VIII before surgical procedures in patients with mild to moderate **haemophilia** or **type I von Willebrand's disease**. The usual dose is 300 or 400 nanograms/kg by slow intravenous infusion over 15 to 30 minutes, or by subcutaneous injection, just before surgery. Further doses may be given, although response is reduced with repeated dosage. It may be used similarly to treat spontaneous or trauma-induced bleeding episodes in these patients. It is also given intranasally in doses of 150 micrograms (in patients weighing less than 50 kg) or 300 micrograms; it should be given 0.5 to 2 hours before surgery. Further doses may be given, although response is reduced with repeated dosage.

For **testing of fibrinolytic response** desmopressin acetate may be given by intravenous infusion in doses of 300 or 400 nanograms/kg over 20 minutes, or by subcutaneous injection in a dose of 300 nanograms/kg. A sample of venous blood is taken 20 minutes after completing the infusion and tested for fibrinolytic activity on fibrin plates. Alternatively, a dose of 300 micrograms may be given intranasally 60 minutes before collecting the blood sample.

For details of uses and doses in children, see below.

Administration in children. Although some desmopressin preparations are licensed in the UK and the USA for paediatric use, the indications are generally fewer than for adults and the age ranges are often not specified.

The *BNFC*, however, lists doses for both licensed and unlicensed indications, and the full range of doses, given according to age, is as follows:

Treatment of diabetes insipidus

orally

- neonate: initially 1 to 4 micrograms 2 or 3 times daily, adjusted according to response
- 1 month to 2 years: initially 10 micrograms 2 or 3 times daily, adjusted according to response (range 30 to 150 micrograms daily)
- 2 to 12 years: initially 50 micrograms 2 or 3 times daily, adjusted according to response (range 100 to 800 micrograms daily)
- 12 to 18 years: initially 100 micrograms 2 or 3 times daily, adjusted according to response (range 200 to 1200 micrograms daily)

sublingually

- 2 to 18 years: initially 60 micrograms 3 times daily, adjusted according to response (range 40 to 240 micrograms 3 times daily)

intranasally

- neonate: initially 100 to 500 nanograms, adjusted according to response (range 1.25 to 10 micrograms daily as a single dose or in 2 divided doses)
- 1 month to 2 years: initially 2.5 to 5 micrograms once or twice daily, adjusted according to response
- 2 to 12 years: initially 5 to 20 micrograms once or twice daily, adjusted according to response
- 12 to 18 years: initially 10 to 20 micrograms once or twice daily, adjusted according to response

subcutaneously or *intramuscularly*

- neonate: initially 100 nanograms once daily, adjusted according to response (use the intramuscular route only)
- 1 month to 12 years: initially 400 nanograms once daily, adjusted according to response
- 12 to 18 years: initially 1 to 4 micrograms once daily, adjusted according to response

Test for suspected diabetes insipidus

intranasally

- 1 month to 2 years: 5 to 10 micrograms as a single dose (although this test is not usually recommended in young children)
- 2 to 12 years: 10 to 20 micrograms as a single dose
- 12 to 18 years: 20 micrograms as a single dose

subcutaneously or *intramuscularly*

- 1 month to 2 years: 400 nanograms as a single dose (although this test is not usually recommended in young children)
- 2 to 12 years: 0.5 to 1 microgram as a single dose
- 12 to 18 years: 1 to 2 micrograms as a single dose

Testing of renal function

intranasally

- 1 month to 1 year: 10 micrograms
- 1 to 15 years: 20 micrograms
- 15 to 18 years: 40 micrograms

subcutaneously or *intramuscularly*

- 1 month to 1 year: 400 nanograms
- 1 to 18 years: 2 micrograms

Test of antidiuretic hormone secretion (congenital deficiency suspected)

intranasally

- 1 month to 2 years: initially 100 to 500 nanograms as a single dose

Test of antidiuretic hormone secretion (congenital deficiency not suspected)

intranasally

- 1 month to 2 years: 1 to 5 micrograms as a single dose

Primary nocturnal enuresis

orally

- 5 to 18 years: 200 micrograms at bedtime, increased if necessary to 400 micrograms

sublingually

- 5 to 18 years: 120 micrograms at bedtime, increased if necessary to 240 micrograms

The need for continued treatment with either route should be reassessed after 3 months by withdrawing desmopressin for at least 1 week

Mild to moderate **haemophilia** or **von Willebrand's disease**

intravenously (infusion over 20 minutes) or *subcutaneously*

- 1 month to 18 years: 300 nanograms/kg as a single dose immediately before surgery or after trauma; the dose may be repeated at intervals of 12 hours if no tachycardia occurs

intranasally

- 1 to 18 years: 4 micrograms/kg as a single dose; for pre-operative use give 2 hours before the procedure

Testing of fibrinolytic response

intravenously (infusion over 20 minutes) or *subcutaneously*

- 2 to 18 years: 300 nanograms/kg as a single dose; blood is sampled after 20 minutes for fibrinolytic activity

Administration in renal impairment. While most UK licensed product information recommends caution when using desmopressin in patients with reduced renal function, *Desmospray (Ferring, UK)* and US licensed product information contra-indicates its use in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50 mL/min). This contra-indication has been questioned,[1] as the risk of hyponatraemia usually associated with desmopressin (see Effects on Electrolytes, p. 2356.3) is reduced in chronic kidney disease. This is due to a loss of urinary-concentrating ability (reducing the diuretic effect of desmopressin), and a limited volume of filtered water for the desmopressin to act on. Adjusting the dose according to response has been suggested as a suitable way of giving desmopressin to patients with chronic kidney disease.

1. Sica DA, Gehr TWB. Desmopressin: safety considerations in patients with chronic renal disease. *Drug Safety* 2006; 29: 553–6.

Diabetes insipidus. Desmopressin is the usual treatment for cranial diabetes insipidus (p. 2348.2).

Haemorrhagic disorders. Desmopressin is used in the management of patients with mild haemophilia A, carriers of haemophilia with low factor VIII concentrations, and patients with acquired haemophilia who have low titres of antibodies to factor VIII (see Haemophilias, p. 1126.3). Desmopressin is also used in von Willebrand's disease (p. 1129.3). The use of desmopressin results in a two- to sixfold increase in plasma concentrations of factor VIII and von Willebrand factor,[1] and patients must have measurable baseline concentrations of these factors in order to respond to desmopressin.[1,2] In general, a baseline factor VIII concentration of 0.1 to 0.15 units/mL is needed to achieve post-injection concentrations of about 0.3 to 0.5 units/mL, which are generally sufficient for minor bleeding or lesser procedures. Concentrations of at least 0.7 to 1 unit/mL must be achieved for major surgery.[1] Desmopressin can be given subcutaneously, but the peak levels of factor VIII are reached later than after intra-

venous use. Intranasal use is also effective and allows patients to treat bleeding episodes themselves, without delay, outside hospital.[1] The use of desmopressin as an alternative to blood products has been recommended whenever possible in the treatment of these disorders, as a precaution against blood-borne infection.[1]

Bleeding due to liver disease has been controlled by desmopressin,[3,4] as has that associated with uraemia[5-8] (but for a report of tolerance to the effects of repeated doses of desmopressin in uraemic patients, see under Adverse Effects and Precautions, p. 2357.1), and there are reports of bleeding being controlled in other disorders such as telangiectasia[9] and platelet storage deficiency.[10-12] See also Haemorrhagic Disorders in Vasopressin (p. 2643.3), and Variceal Haemorrhage in Vasopressin (p. 2643.3) and Terlipressin (p. 2627.2). Desmopressin has also been tried for excessive or heavy menstrual bleeding with mixed results.[13]

Desmopressin has also had conflicting results in surgical procedures.[2] A meta-analysis, which mainly included studies in cardiac surgery, found no evidence that desmopressin reduces perioperative blood transfusion in patients who do not have congenital bleeding disorders.[14] A possible role for desmopressin has been proposed in the control of surgical bleeding in patients whose religious beliefs preclude the use of blood products.[15,16] It has also been reported to be effective in postoperative aspirin-related bleeding that was previously unresponsive to clotting factors.[17] However, studies of prophylactic desmopressin given to patients who had received aspirin in the 7 days before cardiac bypass surgery have produced conflicting results, with desmopressin either reducing blood loss[18] or having no effect.[19]

1. Lethagen S. Desmopressin in mild hemophilia A: indications, limitations, efficacy, and safety. *Semin Thromb Hemost* 2003; **29**: 101–5.
2. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; **90**: 2515–21.
3. Burroughs AK, *et al.* Desmopressin and bleeding time in patients with cirrhosis. *BMJ* 1985; **291**: 1377–81.
4. Rak K, *et al.* Desmopressin and bleeding time in patients with cirrhosis. *BMJ* 1986; **292**: 138.
5. Mannucci PM, *et al.* Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983; **308**: 8–12.
6. Shapiro MD, Kelleher SP. Intranasal deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *Am J Nephrol* 1984; **4**: 260–1.
7. Viganò GL, *et al.* Subcutaneous desmopressin (DDAVP) shortens the bleeding time in uremia. *Am J Hematol* 1989; **31**: 32–5.
8. Jacquot C, *et al.* Addition of desmopressin to recombinant human erythropoietin in treatment of haemostatic defect of uraemia. *Lancet* 1988; **i**: 420.
9. Quitt M, *et al.* The effect of desmopressin on massive gastrointestinal bleeding in hereditary telangiectasia unresponsive to treatment with cryoprecipitate. *Arch Intern Med* 1990; **150**: 1744–6.
10. Nieuwenhuis HK, Sixma JJ. 1-Desamino-8-D-arginine vasopressin (desmopressin) shortens the bleeding time in storage pool deficiency. *Ann Intern Med* 1988; **108**: 65–7.
11. Castaman G, Rodeghiero F. Consistency of responses to separate desmopressin infusions in patients with storage pool disease and isolated prolonged bleeding time. *Thromb Res* 1993; **69**: 407–12.
12. Zatik J, *et al.* Variable response of Hermansky-Pudlak syndrome to prophylactic administration of 1-desamino 8o-arginine in subsequent pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2002; **104**: 165–6.
13. Fraser IS, *et al.* A benefit-risk review of systemic haemostatic agents, part 2: in excessive or heavy menstrual bleeding. *Drug Safety* 2008; **31**: 275–82.
14. Carless PA, *et al.* Desmopressin for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 15/09/05).
15. Martens PR. Desmopressin and Jehovah's witness. *Lancet* 1989; **i**: 1322.
16. Beholz S, *et al.* Use of desmopressin and erythropoietin in an anaemic Jehovah's Witness patient with severely impaired coagulation capacity undergoing stentless aortic valve replacement. *Perfusion* 2001; **16**: 485–9.
17. Chard RB, *et al.* Use of desmopressin in the management of aspirin-related and intractable haemorrhage after cardiopulmonary bypass. *Aust N Z J Surg* 1990; **60**: 125–8.
18. Sheridan DP, *et al.* Use of desmopressin acetate to reduce blood transfusion requirements during cardiac surgery in patients with acetylsalicylic-acid-induced platelet dysfunction. *Can J Surg* 1994; **37**: 33–6.
19. Pleym H, *et al.* Prophylactic treatment with desmopressin does not reduce postoperative bleeding after coronary surgery in patients treated with aspirin before surgery. *Anesth Analg* 2004; **98**: 578–84.

Nocturnal enuresis. Desmopressin is one of the main drugs used as an alternative or adjunct to nonpharmacological methods for the treatment of nocturnal enuresis in children (p. 2349.1). Secretion of vasopressin during the night in normal individuals reduces urine output and it has been suggested that nocturnal enuresis in some children might be due to impaired nocturnal secretion of vasopressin. However, other possible mechanisms include bladder instability and reduced nightly functional bladder capacity, and it has been proposed that treatment should be based on a greater consideration of nocturnal enuresis as a multifactorial condition.[1]

The synthetic vasopressin analogue desmopressin is used for its presumed antidiuretic effect on the kidney,[2] although there is some evidence that it may act by some other mechanism, possibly having a central effect.[3,4] It has been shown that desmopressin given at night can be effective in the short-term control of nocturnal enuresis[2,5] and many now consider it to be the drug of choice in terms of safety.[6,7] There is some evidence[8,9] that long-term use of desmopressin is also effective. However, a meta-analysis suggested that benefit might not be sustained once the drug was stopped.[10] Desmopressin should not be given when enuresis is due to polydipsia as it may provoke water intoxication and convulsions due to hyponatraemia. For precautions to be observed when desmopressin is used to treat enuresis, and the view that nasal formulations should not be used for this indication, see Effects on Electrolytes, below.

1. Butler RJ, *et al.* Investigating the three systems approach to complex childhood nocturnal enuresis. *Scand J Urol Nephrol* 2004; **38**: 117–21.
2. Müller D, *et al.* Comparative tolerability of drug treatment for nocturnal enuresis in children. *Drug Safety* 2004; **27**: 717–27.
3. Jonat S, *et al.* Effect of DDAVP on nocturnal enuresis in a patient with nephrogenic diabetes insipidus. *Arch Dis Child* 1999; **81**: 57–9.
4. Müller D, *et al.* Desmopressin for nocturnal enuresis in nephrogenic diabetes insipidus. *Lancet* 2002; **359**: 495–7.
5. Moffat MEK, *et al.* Desmopressin acetate and nocturnal enuresis: how much do we know? *Pediatrics* 1993; **92**: 420–5.
6. Van de Walle J, *et al.* Is there still a role for desmopressin in children with primary monosymptomatic nocturnal enuresis? A focus on safety issues. *Drug Safety* 2010; **33**: 261–71.
7. NICE. Nocturnal enuresis: the treatment of bedwetting in children and young people (issued October 2010). Available at: http://www.nice.org.uk/nicemedia/live/13246/51367/51367.pdf (accessed 18/11/10)
8. Hjälmås K, *et al.* Long-term treatment with desmopressin in children with primary monosymptomatic nocturnal enuresis: an open multicentre study. *Br J Urol* 1998; **82**: 704–9.
9. Wolfish NM, *et al.* The Canadian Enuresis Study and Evaluation: short- and long-term safety and efficacy of an oral desmopressin preparation. *Scand J Urol Nephrol* 2003; **37**: 22–7.
10. Glazener CMA, Evans JHC. Desmopressin for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 15/09/05).

Orthostatic hypotension. The first drug tried in patients with orthostatic hypotension (p. 1634.3) who cannot be managed by nonpharmacological methods is usually fludrocortisone, but desmopressin is sometimes useful in patients with central neurological abnormalities.[1]

1. Mathias CJ, *et al.* The effect of desmopressin on nocturnal polyuria, overnight weight loss, and morning postural hypotension in patients with autonomic failure. *BMJ* 1986; **293**: 353–4.

Post-dural puncture headache. Desmopressin acetate is licensed for use in the UK subcutaneously or intramuscularly for the treatment or prophylaxis of headache due to lumbar puncture. However, published evidence to support this appears to be scanty, and many patients respond to conservative treatment (see p. 1979.1).

References.

1. Durward WF, Harrington H. Headache after lumbar puncture. *Lancet* 1976; **ii**: 1403–4.
2. Widerlöv E, Lindström L. DDAVP and headache after lumbar puncture. *Lancet* 1979; **i**: 548.
3. Hansen PE, Hansen JH. DDAVP, a synthetic analogue of vasopressin, in prevention of headache after lumbar puncture and lumbar pneumoencephalography. *Acta Neurol Scand* 1979; **60**: 183–8.
4. Cowan JMA, *et al.* DDAVP in the prevention of headache after lumbar puncture. *BMJ* 1980; **280**: 224.

Renal colic. Intranasal desmopressin is being studied[1] in the management of the pain of acute renal colic (p. 6.3).

1. Zabihi N, Teichman JMH. Dealing with the pain of renal colic. *Lancet* 2001; **358**: 437–8.

Urinary incontinence. Desmopressin given intranasally appeared to be effective in reducing voiding frequency/incontinence when studied in 26 patients with multiple sclerosis whose bladder dysfunction had previously been unresponsive to antimuscarinics;[1] similar results have been reported in other small studies in patients with multiple sclerosis.[2] However, a review of studies using desmopressin to treat nocturia in such patients cast doubt on the clinical relevance of the limited reductions achieved in voiding frequency.[3] Nevertheless, beneficial long-term use of desmopressin for nocturia has been described, with some patients also using it intermittently during the daytime to control symptoms for special occasions.[4] Oral desmopressin has been reported to have a favourable effect on measures such as the number of nocturnal voids and duration of sleep until the first nocturnal void in women[5] and men[6] with nocturia. Beneficial effects were maintained or improved in many responders who were treated for a further 10 or 12 months.[7] In the management of daytime urinary incontinence in women, an improvement in the incidence of periods without leakage during the 4 hours after an intranasal dose of desmopressin has been reported.[8]

For the usual treatment of incontinence, see Urinary Incontinence and Retention, p. 2349.2.

1. Fredrikson S. Nasal spray desmopressin treatment of bladder dysfunction in patients with multiple sclerosis. *Acta Neurol Scand* 1996; **94**: 31–4.
2. Cvetković RS, Plosker GL. Desmopressin: in adults with nocturia. *Drugs* 2005; **65**: 99–107.
3. Ferreira E, Letwin SR. Desmopressin for nocturia and enuresis associated with multiple sclerosis. *Ann Pharmacother* 1998; **32**: 114–16.
4. Tubridy N, *et al.* Long term use of desmopressin for urinary symptoms in multiple sclerosis. *Multiple Sclerosis* 1999; **5**: 416–17.
5. Lose G, *et al.* Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. *Am J Obstet Gynecol* 2003; **189**: 1106–13.
6. Mattiasson A, *et al.* Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. *BJU Int* 2002; **89**: 855–62.
7. Lose G, *et al.* Clinical experiences with desmopressin for long-term treatment of nocturia. *J Urol (Baltimore)* 2004; **172**: 1021–5.
8. Robinson D, *et al.* Antidiuresis: a new concept in managing female daytime urinary incontinence. *BJU Int* 2004; **93**: 996–1000.

Adverse Effects and Precautions

Adverse effects of desmopressin include headache, nausea, and mild abdominal cramps; there may be pain and swelling at the site of injection. With large intravenous doses hypotension, with tachycardia and facial flushing, may occur; some patients may experience an increase in blood pressure. Occasionally there may be cerebral or coronary thrombosis. Hypersensitivity reactions have also occurred. The antidiuretic action of desmopressin can produce water intoxication and hyponatraemia, occasionally leading to convulsions. The incidence of hyponatraemia may be higher with nasal formulations than with oral formulations. Nasal doses may cause local irritation, congestion, and epistaxis.

Precautions to be observed with desmopressin are similar to those for vasopressin (see p. 2644.1). It should not be given to patients with type IIB von Willebrand's disease, in whom the release of clotting factors may lead to platelet aggregation and thrombocytopenia. Caution is required with patients who have impaired renal function, see Administration in Renal Impairment, p. 2355.3. When desmopressin is used diagnostically, or for the treatment of enuresis, the fluid intake should be limited to a minimum and only to satisfy thirst from 1 hour before to 8 hours after use (see also Effects on Electrolytes, below).

Effects on the cardiovascular system. Facial flushing and warmth after intravenous desmopressin reflect a vasodilator action[1] or may be due to an opioid mechanism in the CNS.[2] A drop in diastolic blood pressure of about 14 mmHg and an increase in heart rate of 20 beats/minute are the rule during intravenous infusion of desmopressin in doses of 400 nanograms/kg or more.[1] The hypotensive effects of desmopressin were responsible for a serious reaction, involving cyanosis and dyspnoea, in a 21-month-old child with cyanotic heart disease.[3] Thrombosis (including myocardial infarction)[4-6] and cerebral infarction[7] have been associated rarely with the use of intravenous desmopressin. An analysis[8] of events in patients undergoing major surgery suggested, however, that co-existing conditions in elderly patients and the surgical procedures themselves were associated with a high risk of thrombosis, and that desmopressin did not increase the incidence of thrombotic events.

Licensed product information also warns of the possibility of an increase in blood pressure.

1. Brommer EJP, *et al.* Desmopressin and hypotension. *Ann Intern Med* 1985; **103**: 962.
2. Pigache RM. Facial flushing induced by vasopressin-like peptides lacking pressor activity. *J Clin Pharmacol* 1984; **17**: 369–71.
3. Israels SJ, Kobrinsky NL. Serious reaction to desmopressin in a child with cyanotic heart disease. *N Engl J Med* 1989; **320**: 1563–4.
4. Anonymous. Desmopressin and arterial thrombosis. *Lancet* 1989; **i**: 938–9.
5. Mannucci PM, Lusher JM. Desmopressin and thrombosis. *Lancet* 1989; **ii**: 675–6.
6. Hartmann S, Reinhart W. Fatal complication of desmopressin. *Lancet* 1995; **345**: 1302–3. Correction. *ibid.*: 1648.
7. Grunwald Z, Sather SDC. Intraoperative cerebral infarction after desmopressin administration in infant with end-stage renal disease. *Lancet* 1995; **345**: 1364–5.
8. Mannucci PM, *et al.* Desmopressin, surgery and thrombosis. *Thromb Haemost* 1994; **71**: 154–5.

Effects on electrolytes. There have been a number of reports of seizures due to hyponatraemia and water intoxication after intranasal[1-8] or intravenous[9] desmopressin. The UK CSM noted in March 1996 that it had received reports of hyponatraemic convulsions in 21 children and 3 adults receiving desmopressin (which it somewhat inaccurately described as vasopressin).[10] It was recommended that when this drug was used to treat primary nocturnal enuresis the risks of hyponatraemia should be minimised by

- avoiding concomitant use of drugs, such as *tricyclic antidepressants*, that increase endogenous ADH secretion
- keeping to the recommended starting dose
- avoiding excessive fluid intake, including ingestion of water during swimming
- stopping treatment temporarily if vomiting or diarrhoea occurred, to allow recovery of normal fluid and electrolyte balance

Some have suggested that no more than 240 mL of fluid should be ingested on nights when desmopressin is given.[7] Others have suggested that serum-sodium concentrations be measured 24 to 48 hours, 1 week, and 1 month after starting treatment with desmopressin.[8] A systematic review[11] of the risk in older patients being treated for nocturia, which found the incidence of hyponatraemia to be about 8%, also recommended regular monitoring. Others[12] have gone further and do not recommend desmopressin be used to treat nocturia or nocturnal polyuria in frail or elderly patients.

In April 2007, the MHRA requested that the indication for the treatment of primary nocturnal enuresis be removed from desmopressin nasal spray formulations in the UK. Compared with oral formulations, nasal forms were associated with most of the serious adverse effects reported in patients with primary nocturnal enuresis; these included hyponatraemia, water intoxication, and convulsions. Hyponatraemia was reported at a rate of about 15 cases per 100 000 years of patient exposure for nasal dosage forms, compared with 6 cases per 100 000 patient years for oral formulations; hyponatraemia was mainly associated with overdose, excessive fluid intake, or inappropriate use.[13] Similar warnings have been issued by other regulatory authorities, including the FDA.[14]

1. Simmonds EJ, *et al.* Convulsions and coma after intranasal desmopressin in cystic fibrosis. *BMJ* 1988; 297: 1614.
2. Salvatoni A, *et al.* Hyponatremia and seizures during desmopressin acetate treatment in hypothyroidism. *J Pediatr* 1990; 116: 835–6.
3. Davis RC, *et al.* Nocturnal enuresis. *Lancet* 1992; 340: 1550.
4. Hamed M, *et al.* Hyponatraemic convulsion associated with desmopressin and imipramine treatment. *BMJ* 1993; 306: 1169.
5. Hourihane J, Salisbury AJ. Use caution in prescribing desmopressin for nocturnal enuresis. *BMJ* 1993; 306: 1545.
6. Robson WLM, Leung AKC. Hyponatraemia following desmopressin. *BMJ* 1993; 307: 64–5.
7. Robson WLM, *et al.* Hyponatremia in patients with nocturnal enuresis treated with DDAVP. *Eur J Pediatr* 1996; 155: 959–62.
8. Odeh M, Oliven A. Coma and seizures due to severe hyponatremia and water intoxication in an adult with intranasal desmopressin therapy for nocturnal enuresis. *J Clin Pharmacol* 2001; 41: 582–4.
9. Shepherd LL, *et al.* Hyponatremia and seizures after intravenous administration of desmopressin acetate for surgical hemostasis. *J Pediatr* 1989; 114: 470–2.
10. CSM/MCA Hyponatraemic convulsions in patients with enuresis treated with vasopressin. *Current Problems* 1996; 22: 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20244586-RevisionSelectionMethod=LatestReleased (accessed 21/01/09)
11. Weatherall M. The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and meta-analysis. *Neurourol Urodyn* 2004; 23: 302–5.
12. Schröder A, *et al.* European Association of Urology. Guidelines on urinary incontinence (updated April 2010). Available at: http://www.uroweb.org/gls/pdf/16_Urinary_Incontinence%202010.pdf (accessed 03/10/11)
13. MHRA. Desmopressin nasal spray: removal of the primary nocturnal enuresis (bedwetting) indication (issued 18th April 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2030795 (accessed 02/09/08)
14. FDA. Information for healthcare professionals: desmopressin acetate (marketed as DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimate Nasal Spray) (issued 4th December 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/desmopressinHCP.htm (accessed 11/06/08)

Effects on the eyes. Pseudotumor cerebri associated with desmopressin treatment has been reported in a patient.[1]

1. Neely DE, *et al.* Desmopressin (DDAVP)-induced pseudotumor cerebri. *J Pediatr* 2003; 143: 808.

Effects on mental function. Paranoid psychosis occurred after desmopressin therapy in a patient with Alzheimer's dementia.[1]

1. Collins GB, *et al.* Paranoid psychosis after DDAVP therapy for Alzheimer's dementia. *Lancet* 1981; ii: 808.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desmopressin 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)

Tolerance. In 3 uraemic patients desmopressin infusion produced an initial shortening of the bleeding time but after repeated infusions this response was reduced and there was even some increase in baseline bleeding times.[1] Two infusions of desmopressin 300 nanograms/kg in one day appear to induce a near maximum response; different treatment is required subsequently.

1. Canavese C, *et al.* Reduced response of uraemic bleeding time to repeated doses of desmopressin. *Lancet* 1985; i: 867–8.

Interactions

As for Vasopressin, p. 2644.2. See also Effects on Electrolytes, p. 2356.3. NSAIDs, such as ibuprofen (see Effects on Electrolytes under Ibuprofen, p. 69.3) and indometacin, may enhance the antidiuretic effect of desmopressin.

Gastrointestinal drugs. In a study[1] in healthy subjects, *loperamide* caused a threefold increase in the gastrointestinal absorption of oral desmopressin, presumably by slowing gastrointestinal motility. In the same study, however, increased motility caused by *erythromycin* did not affect desmopressin absorption.

1. Callréus T, *et al.* Changes in gastrointestinal motility influence the absorption of desmopressin. *Eur J Clin Pharmacol* 1999; 55: 305–9.

Pharmacokinetics

Desmopressin is absorbed from the nasal mucosa with a bioavailability of 10 to 20%. After oral doses it is largely destroyed in the gastrointestinal tract but sufficient is absorbed from high doses to produce therapeutic effects. When given intravenously desmopressin exhibits biphasic pharmacokinetics, with half-lives of about 8 minutes and 75 minutes for the 2 phases respectively.

References.
1. Pjellestad-Paulsen A, *et al.* Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers. *Clin Endocrinol (Oxf)* 1993; 38: 177–82.
2. Lam KSL, *et al.* Pharmacokinetics, pharmacodynamics, long-term efficacy and safety of oral 1-deamino-8-D-arginine vasopressin in adult patients with central diabetes insipidus. *Br J Clin Pharmacol* 1996; 42: 379–85.
3. Agersø H, *et al.* Pharmacokinetics and renal excretion of desmopressin after intravenous administration to healthy subjects and renally impaired patients. *Br J Clin Pharmacol* 2004; 58: 352–8.
4. Østerberg O, *et al.* Pharmacokinetics of desmopressin administrated [sic] as an oral lyophilisate dosage form in children with primary nocturnal enuresis and healthy adults. *J Clin Pharmacol* 2006; 46: 1204–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Emosint; Octostim; Presinex; *Austral.*: Minirin; Octostim; *Austria*: Minirin; Nocutil; Octostim; *Belg.*: Minirin; Octostim; *Braz.*: D-Void; DDAVP; *Canad.*: DDAVP; Minirin; Octostim; *Chile*: DDAVP; Desmo-C; Octostim; *China*: Minirin (弥行); *Cz.*: Desmospray†; Desmotabs†; Minirin; *Denm.*: Desmoham; DesmoMelt; Desmopal; Minirin; Minirinmelt; Minurin; Nocutil; Octostim; *Fin.*: Minirin; Octostim; *Fr.*: Minirin; Minirinmelt; Octim; *Ger.*: Desmogalen; Desmospray; Desmotabs; Minirin; Nocturin; Nocutil; Octostim; *Gr.*: DDAVP; Defirin; Desmoprol; Esmon; Minirin; *Hong Kong*: Minirin; Octostim; *Hung.*: Desmopress†; Minirin; Nocutil; Octostim; *India*: D-Pressin; D-Void; Des-Press; Minirin; *Irl.*: DDAVP; Desmospray; Desmotabs; Nordurine; *Israel*: Adin†; Minirin; Octostim; *Ital.*: Emosint; Minirin/DDAVP; *Jpn*: Minirinmelt; *Malaysia*: Minirin; *Mex.*: Minirin; Nafiset; Octostim; *Neth.*: Adiuretin†; Minirin†; Minrin; Octostim; *Norw.*: Minirin; Octostim; *NZ*: Minirin; Octostim; *Philipp.*: Minirin; Octostim; *Pol.*: Minirin; Noctissin; *Port.*: DDAVP; Desmospray; Minirin; Presinex; *Rus.*: Emosint (Эмосинт); Minirin (Минирин); Presinex (Пресайнекс); *S.Afr.*: DDAVP; *Singapore*: Minirin; *Spain*: Minurin; Octostim; Wetirin; *Swed.*: Minirin; Nocutil; Octostim; *Switz.*: Minirin; Nocutil; Octostim; *Thai.*: Minirin; *Turk.*: Desmovital; Minirin; Octostim; *UK*: DDAVP; DesmoMelt; Desmospray; Desmotabs; Octim; Presinex†; *Ukr.*: Adiupressin (Адиупрессин); Minirin (Минирин); Uropres (Уропрес); *USA*: DDAVP; Minirin; Stimate.

Pharmacopoeial Preparations
BP 2014: Desmopressin Injection; Desmopressin Intranasal Solution; Desmopressin Tablets;
USP 36: Desmopressin Acetate Injection; Desmopressin Nasal Spray Solution.

Dutasteride *(BAN, USAN, rINN)*

Dutasterid; Dutasterida; Dutastéride; Dutasteridum; GG-745; GI-198745; GI-198745X; Дутастерид.
α,α,α,α′,α′,α′-Hexafluoro-3-oxo-4-aza-5α-androst-1-ene-17β-carboxy-2′,5′-xylidide; 3-Oxo-2′,5′-bis(trifluoromethyl)-4-aza-5α-androst-1-ene-17β-carboxanilide.
$C_{27}H_{30}F_6N_2O_2$=528.5
CAS — 164656-23-9.
ATC — G04CB02.
ATC Vet — QG04CB02.
UNII — C0J6XJN02I.

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

Ph. Eur. 8: (Dutasteride). A white or pale yellow powder. Practically insoluble in water; soluble or sparingly soluble in anhydrous alcohol; freely soluble in dichloromethane.

Uses and Administration

Dutasteride, like finasteride (p. 2358.3), is an inhibitor of 5α-reductase. Unlike finasteride, it is claimed to inhibit both the type-1 and type-2 isoforms of the enzyme. Dutasteride is used in the treatment of benign prostatic hyperplasia (p. 2347.1); it may reduce the incidence of acute urinary retention and the need for surgery. Dutasteride is given in oral doses of 500 micrograms daily, either alone or with the alpha-blocker tamsulosin (p. 2369.1). Response may be delayed and treatment for 6 months may be required to assess whether benefit has been achieved.

Dutasteride is under investigation for the prevention of prostate cancer, and in the treatment of alopecia.

References.
1. Djavan B, *et al.* Dutasteride: a novel dual inhibitor of 5alpha-reductase for benign prostatic hyperplasia. *Expert Opin Pharmacother* 2005; 6: 311–17. Correction. *ibid.*; 681.
2. Dolder CR. Dutasteride: a dual 5-α reductase inhibitor for the treatment of symptomatic benign prostatic hyperplasia. *Ann Pharmacother* 2006; 40: 658–64.
3. Keam SJ, Scott LJ. Dutasteride: a review of its use in the management of prostate disorders. *Drugs* 2008; 68: 463–85.
4. Fenter TC, *et al.* Dutasteride vs finasteride: assessment of differences in acute urinary retention rates and surgical risk outcomes in an elderly population aged ⩾ 65 years. *Am J Manag Care* 2008; 14 (suppl 2): S154–S159.
5. Musquera M, *et al.* The REDUCE trial: chemoprevention in prostate cancer using a dual 5 α -reductase inhibitor, dutasteride. *Expert Rev Anticancer Ther* 2008; 8: 1073–9.
6. Rittmaster R, *et al.* Effect of dutasteride on intraprostatic androgen levels in men with benign prostatic hyperplasia or prostate cancer. *Urology* 2008; 72: 808–12.
7. Roehrborn CG, *et al.* CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur Urol* 2010; 57: 123–31.
8. Andriole GL, *et al.* REDUCE Study Group. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010; 362: 1192–1202.

Adverse Effects and Precautions

As for Finasteride, p. 2359.2 and p. 2359.3.

Interactions

Dutasteride is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5. Dutasteride concentrations may be increased by moderate or potent inhibitors of CYP3A4 and a reduction of the dutasteride dosing frequency may be considered if adverse effects are noted.

Pharmacokinetics

Dutasteride is absorbed from the gastrointestinal tract, reaching a peak serum concentration in 1 to 3 hours, with a bioavailability of about 60%. It is highly bound to plasma proteins. Dutasteride is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, and most of a dose is excreted as metabolites in the faeces. At steady state the elimination half-life is about 3 to 5 weeks.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Avodart; *Austral.*: Avodart; *Austria*: Avodart; Avolve†; *Belg.*: Avodart; *Braz.*: Avodart; *Canad.*: Avodart; *Chile*: Avodart; *Cz.*: Avodart; *Denm.*: Avidart; Avodart; Duagen; *Fin.*: Avodart; *Fr.*: Avodart; *Ger.*: Avodart; *Gr.*: Avodart; Duagen; *Hong Kong*: Avodart; *Hung.*: Avodart; *India*: Duprost; Dutagen; Dutas; *Indon.*: Avodart; *Irl.*: Avodart; *Israel*: Avodart; *Ital.*: Avodart; Duagen; *Malaysia*: Avodart; *Mex.*: Avodart; *Neth.*: Avodart; *Norw.*: Avodart; *Philipp.*: Avodart; *Pol.*: Avodart†; *Port.*: Avodart; Avolve†; Duagen; *Rus.*: Avodart (Аводарт); *S.Afr.*: Avodart; *Singapore*: Avodart; *Spain*: Avidart; Duagen†; *Swed.*: Avodart; *Switz.*: Avodart; *Thai.*: Avodart; *Turk.*: Avodart; *UK*: Avodart; *Ukr.*: Avodart (Аводарт); *USA*: Avodart.

Multi-ingredient Preparations. *Austral.*: Duodart; *Belg.*: Combodart; *Canad.*: Jalyn; *Cz.*: Duodart; *Denm.*: Combodart; *Fin.*: Duodart; *Ger.*: Duodart; *Gr.*: Duodart; *India*: Afdura; Dutalfa; Dutas-T; *Irl.*: Combodart; *Israel*: Duodart; *Neth.*: Combodart; *Norw.*: Duodart; *Pol.*: Duodart; *Port.*: Combodart; *Spain*: Duodart; *Switz.*: Duodart; *UK*: Combodart; *USA*: Jalyn.

Elocalcitol *(rINN)*

BXL-628; Elocalcitol; Elocalcitolum; Элькальцитол.
(1*S*,3*R*,5*Z*,7*E*,23*E*)-1-Fluoro-26,27-dihomo-9,10-secocholesta-5,7,10(19),16,23-pentaene-3,25-diol.
$C_{29}H_{43}FO_2$=442.7
CAS — 199798-84-0.
UNII — 2WDS5F2V6Q.

NOTE. Do not confuse with eldecalcitol (p. 1182.3).

Profile

Elocalcitol is a derivative of vitamin D (p. 2112.3) that is under investigation for benign prostatic hyperplasia, overactive bladder, and male infertility.

References.
1. Tiwari A. Elocalcitol, a vitamin D3 analog for the potential treatment of benign prostatic hyperplasia, overactive bladder and male infertility. *IDrugs* 2009; 12: 381–93.

Emepronium Bromide *(BAN, rINN)*

Bromuro de emepronio; Emepronii Bromidum; Emepronio, bromuro de; Émépronium, Bromure d'; Emeproniumbromid; Emeproniumbromidi; Эмепрония бромид.
Ethyldimethyl(1-methyl-3,3-diphenylpropyl)ammonium bromide.
$C_{20}H_{28}BrN$=362.4
CAS — 27892-33-7 (emepronium); 3614-30-0 (emepronium bromide).
ATC — G04BD01.
ATC Vet — QG04BD01.
UNII — WZM699L2TL.

The symbol † denotes a preparation no longer actively marketed

Emepronium Carrageenate (BAN)

Emepronio, carragenato de.
ATC — G04BD01.
ATC Vet — QG04BD01.

Uses and Administration

Emepronium is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1310.3). It has been used orally as the bromide and the carrageenate in the treatment of urinary frequency and incontinence (p. 2349.2); the bromide has also been given by subcutaneous or intramuscular injection.

Urinary incontinence. In the UK, guidelines issued by NICE suggest that emepronium should not be recommended for the treatment of urinary incontinence or overactive bladder in women; other antimuscarinics are preferred.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2.

To avoid oesophageal ulceration, tablets of emepronium bromide should always be swallowed with an adequate volume of water, and patients should always be in the sitting or standing position while, and for 10 to 15 minutes after, taking the tablets. Emepronium is contra-indicated in patients with symptoms or signs of oesophageal obstruction or with pre-existing oesophagitis.

Buccal and oesophageal ulceration. Tablet-induced oesophageal damage is a widely recognised problem and is related to direct mucosal injury by the medication. Emepronium bromide has been frequently implicated in this type of mucosal injury, although it rarely results in stricture formation.[1]

1. McCord GS, Clouse RE. Pill-induced esophageal strictures: clinical features and risk factors for development. *Am J Med* 1990; **88:** 512–18.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies emepronium 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

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Emepronium is incompletely absorbed from the gastrointestinal tract and is mainly excreted unchanged in the urine and faeces. It does not readily cross the blood-brain barrier at therapeutic doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Urikrat Novum.

Fesoterodine (BAN, rINN)

Fesoterodina; Fésotérodine; Fesoterodinum; Фезотеродин.
2-[(1*R*)-3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate.
$C_{26}H_{37}NO_3$=411.6
CAS — 286930-02-7.
ATC — G04BD11.
ATC Vet — QG04BD11.
UNII — 621G617227.

Fesoterodine Fumarate (BANM, USAN, rINNM)

Fésotérodine, Fumarate de; Fesoterodini Fumaras; Fumarato de fesoterodina; SPM-907; SPM-8272; Фезотеродина Фумарат.
$C_{26}H_{37}NO_3.C_4H_4O_4$=527.7
CAS — 286930-03-8.
UNII — EOS7216557.

Uses and Administration

Fesoterodine is an antimuscarinic used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome (p. 2349.2). It is given orally as the fumarate; the usual initial dose is 4 mg once daily, increased to a maximum of 8 mg once daily if necessary, according to response. Patients should be re-evaluated after 8 weeks of treatment. In those taking moderate inhibitors of the cytochrome P450 isoenzyme CYP3A4, caution is advised when increasing the dose of fesoterodine fumarate to 8 mg once daily. UK and US licensed product information recommend that the dose of fesoterodine fumarate should not exceed 4 mg once daily in patients taking potent CYP3A4 inhibitors. In those taking CYP2D6 inhibitors, UK licensed product information suggests that the dose of fesoterodine fumarate may need to be reduced to 4 mg once daily. For doses in hepatic and renal impairment, see below.

References.
1. McKeage K, Keating GM. Fesoterodine. *Drugs* 2009; **69:** 731–8.
2. Tzefos M, *et al.* Fesoterodine for the treatment of overactive bladder. *Ann Pharmacother* 2009; **43:** 1992–2000.
3. Herschorn S, *et al.* Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. *BJU Int* 2010; **105:** 58–66.

Administration in hepatic impairment. UK licensed product information for fesoterodine fumarate states that patients with mild hepatic impairment should increase their dose with caution; those also receiving moderate CYP3A4 inhibitors should not exceed an oral dose of fesoterodine fumarate 4 mg once daily, and concomitant potent CYP3A4 inhibitors are not recommended. Patients with moderate impairment (Child-Pugh class B) should not exceed a dose of 4 mg once daily and concomitant moderate or potent CYP3A4 inhibitors are not recommended.

In the USA, no dose adjustments are recommended in patients with mild or moderate hepatic impairment.

Fesoterodine fumarate is contra-indicated in those with severe impairment (Child-Pugh class C), due to a lack of data.

Administration in renal impairment. UK licensed product information for fesoterodine fumarate states that patients with mild (GFR 50 to 80 mL/minute) or moderate (GFR 30 to 50 mL/minute) renal impairment, should increase their dose with caution; those also receiving moderate CYP3A4 inhibitors should not exceed an oral dose of fesoterodine fumarate 4 mg once daily, and concomitant potent CYP3A4 inhibitors are not recommended. Patients with severe impairment (GFR less than 30 mL/minute) should not exceed a dose of 4 mg once daily and concomitant moderate or potent CYP3A4 inhibitors are not recommended.

In the USA, no dose adjustments are recommended in patients with mild or moderate renal impairment; a maximum dose of fesoterodine fumarate 4 mg once daily is recommended in those with severe impairment.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Additional adverse effects reported with fesoterodine include dizziness, headache, increased liver enzyme values, and peripheral oedema. Angina and QT prolongation have been reported. Fesoterodine is contra-indicated in severe hepatic impairment; caution is required when used in patients with mild or moderate hepatic impairment or with renal impairment (see Administration in Hepatic Impairment and Administration in Renal Impairment, above). Caution is needed when used with potent or moderate CYP3A4 inhibitors, potent CYP3A4 inducers, or with potent CYP2D6 inhibitors (see Interactions and Uses and Administration, below and above, respectively). Fesoterodine should not be used in patients with moderate to severe hepatic or renal impairment who are also taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Fesoterodine is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Inhibitors or inducers of these enzymes can affect exposure to fesoterodine; dosage adjustments may be necessary (see Uses and Administration, above).

References.
1. Malhotra B, *et al.* Evaluation of drug-drug interactions with fesoterodine. *Eur J Clin Pharmacol* 2009; **65:** 551–60.

Pharmacokinetics

Fesoterodine is well absorbed orally, and rapidly hydrolysed to its active metabolite (5-hydroxymethyltolterodine) by plasma esterases. Bioavailability of the active metabolite is about 52%. Peak plasma concentrations occur around 5 hours after an oral dose. The active metabolite is about 50% bound to plasma proteins. It is further metabolised in the liver by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolites; none of these metabolites has significant antimuscarinic activity. Exposure to the active metabolite of fesoterodine is higher in patients with hepatic or renal impairment, and in poor metabolisers of CYP2D6 compared with extensive metabolisers. Some 70% of an oral dose of fesoterodine is recovered in the urine as metabolites, and a smaller amount in the faeces. The terminal half-life of the active metabolite is about 7 hours after oral dosing, and about 4 hours after intravenous dosing.

References.
1. Malhotra B, *et al.* Pharmacokinetic profile of fesoterodine. *Int J Clin Pharmacol Ther* 2008; **46:** 556–63.
2. Malhotra B, *et al.* Assessment of the effects of renal impairment on the pharmacokinetic profile of fesoterodine. *J Clin Pharmacol* 2009; **49:** 477–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Toviaz; *Belg.*: Toviaz; *Canad.*: Toviaz; *Cz.*: Toviaz; *Denm.*: Toviaz; *Ger.*: Toviaz; *Gr.*: Toviaz; *Irl.*: Toviaz; *Israel*: Toviaz; *Ital.*: Toviaz; *Jpn*: Toviaz; *Neth.*: Toviaz; *Norw.*: Toviaz; *Pol.*: Toviaz; *Port.*: Toviaz; *Spain*: Toviaz; *Swed.*: Toviaz; *Switz.*: Toviaz; *Turk.*: Toviaz; *UK*: Toviaz; *USA*: Toviaz.

Finasteride (BAN, USAN, rINN)

Finasterid; Finasterida; Finasteridas; Finastéride; Finasteridi; Finasteridum; Finaszterid; MK-0906; MK-906; YM-152; Финастерид.
N-tert-Butyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.
$C_{23}H_{36}N_2O_2$=372.6
CAS — 98319-26-7.
ATC — D11AX10; G04CB01.
ATC Vet — QD11AX10; QG04CB01.
UNII — 57GNO57U7G.

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

Ph. Eur. 8: (Finasteride). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. Protect from light.

USP 36: (Finasteride). A white to off-white crystalline solid. Very slightly soluble in water; freely soluble in alcohol and in chloroform. Store in airtight containers.

Uses and Administration

Finasteride is an azasteroid that inhibits the type-2 isoform of 5α-reductase, the enzyme responsible for conversion of testosterone to the more active dihydrotestosterone, and therefore has anti-androgenic properties. It is given orally in a dose of 5 mg daily in the management of **benign prostatic hyperplasia** to cause regression of the enlarged prostate and to improve symptoms; it may reduce the incidence of acute urinary retention and the need for surgery. Response may be delayed and treatment may be required for 6 months or more to assess whether benefit has been achieved.

In the treatment of **male-pattern baldness** (alopecia androgenetica) in men, finasteride is given orally in a dose of 1 mg daily. In general, use for 3 months or more is required before benefit is seen, and effects are reversed within 12 months of ceasing therapy.

Alopecia. In men with male-pattern baldness (alopecia—see p. 1682.3), treatment with oral finasteride for 12 months resulted in an 11% increase in vertex hair count, which was maintained in those who continued therapy.[1] Extension of this study to 5 years found that long-term treatment with finasteride maintained beneficial effects, or at least slowed hair loss.[2] High baseline concentrations of 5α-dihydrotestosterone predict a good response to treatment with finasteride in patients aged 26 years and under.[3] The use of oral finasteride for male-pattern baldness has been reviewed.[4–6] Some efficacy has also been found with topical finasteride.[7]

Although finasteride is contra-indicated in women who are or may become pregnant (see Precautions, p. 2359.3), a dose of 2.5 mg daily has been used with an oral contraceptive containing drospirenone and ethinylestradiol for female pattern hair loss,[8] with some success. Finasteride has also been investigated in the treatment of male-pattern baldness in postmenopausal women; however, a 1-year placebo-controlled study[9] found no benefit. There have been reports of benefit from finasteride in women with hair loss due to hyperandrogenism[10] or androgen therapy.[11]

1. Kaufman KD, *et al.* Finasteride in the treatment of men with androgenetic alopecia. *J Am Acad Dermatol* 1998; **39:** 578–89.
2. The finasteride male pattern hair loss study group. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. *Eur J Dermatol* 2002; **12:** 38–49.

3. Camacho FM, *et al.* Value of hormonal levels in patients with male androgenetic alopecia treated with finasteride: better response in patients under 26 years old. *Br J Dermatol* 2008; 158: 1121–4.
4. McClellan KJ, Markham A. Finasteride: a review of its use in male pattern hair loss. *Drugs* 1999; 57: 111–26.
5. Whiting DA. Advances in the treatment of male androgenetic alopecia: a brief review of finasteride studies. *Eur J Dermatol* 2001; 11: 332–4.
6. Libecco JF, Bergfeld WF. Finasteride in the treatment of alopecia. *Expert Opin Pharmacother* 2004; 5: 933–40.
7. Mazzarella F, *et al.* Topical finasteride in the treatment of androgenic alopecia. *J Dermatol Treat* 1997; 8: 189–92.
8. Iorizzo M, *et al.* Finasteride treatment of female pattern hair loss. *Arch Dermatol* 2006; 142: 298–302.
9. Price VH, *et al.* Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. *J Am Acad Dermatol* 2000; 43: 768–76.
10. Shum KW, *et al.* Hair loss in women with hyperandrogenism: four cases responding to finasteride. *J Am Acad Dermatol* 2002; 47: 733–9.
11. Hong J-B, *et al.* A woman with iatrogenic androgenetic alopecia responding to finasteride. *Br J Dermatol* 2007; 156: 754–5.

Benign prostatic hyperplasia. Finasteride[1,2] is used in the management of benign prostatic hyperplasia (p. 2347.1). It produces moderate reductions in prostate volume, although this takes a number of months and is not always associated with much symptomatic improvement; therapy must be continued indefinitely for benefit to be maintained. A 4-year study found that finasteride reduced the probability of surgery and acute urinary retention in men with symptomatic benign prostate hyperplasia with prostatic enlargement.[3] Although the need for prostatectomy was reduced by 55% it was pointed out[4] that only 6% of patients would benefit from treatment with finasteride, since for every 100 men treated, 7 finasteride and 13 placebo recipients required surgery. A 2-year, open-label follow-up[5] of this study reported that the reductions in probability of surgery and acute urinary retention were maintained. It was also found that in patients who switched from placebo to finasteride, these measures decreased to become similar to those recorded in men already receiving finasteride. A comparative 12-month study[6] found the alpha blocker terazosin to be more effective than finasteride in relieving symptoms and improving peak urine flow rates; the combination of finasteride plus terazosin was no more effective than terazosin alone. Moreover, although finasteride reduced prostatic volume, it was no more effective than placebo, a finding that is at odds with previous placebo-controlled studies. It has been suggested that the smaller median prostate size in this study may explain the negative findings,[7] and that men with larger prostates do benefit from finasteride. Similar results were reported in a 12-month study using doxazosin.[8] Later results[9,10] from a large study showed that over a longer period of 4 or more years the combination of doxazosin and finasteride reduced the risk of clinical progression more than either drug alone. The combination of an alpha blocker and 5α-reductase inhibitor is therefore considered to be a suitable option for patients with urinary symptoms and demonstrable prostatic enlargement, and who are at significant risk of progression.

1. Wilde MI, Goa KL. Finasteride: an update of its use in the management of symptomatic benign prostatic hyperplasia. *Drugs* 1999; 57: 557–81.
2. Smith AB, Carson CC. Finasteride in the treatment of patients with benign prostatic hyperplasia: a review. *Ther Clin Risk Manag* 2009; 5: 535–45.
3. McConnell JD, *et al.* The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostate hyperplasia. *N Engl J Med* 1998; 338: 557–63.
4. Wasson JH. Finasteride to prevent morbidity from benign prostatic hyperplasia. *N Engl J Med* 1998; 338: 612–13.
5. Roehrborn CG, *et al.* Sustained decrease in incidence of acute urinary retention and surgery with finasteride for 6 years in men with benign prostatic hyperplasia. *J Urol (Baltimore)* 2004; 171: 1194–8.
6. Lepor H, *et al.* The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med* 1996; 335: 533–9.
7. Walsh PC. Treatment of benign prostatic hyperplasia. *N Engl J Med* 1996; 335: 586–7.
8. Kirby RS, *et al.* Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* 2003; 61: 119–26.
9. McConnell JD, *et al.* The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; 349: 2387–98.
10. Kaplan SA, *et al.* Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia in patients with lower urinary tract symptoms and a baseline total prostate volume of 25 ml or greater. *J Urol (Baltimore)* 2006; 175: 217–20.

Hirsutism. Finasteride is reported to be effective for the treatment of hirsutism (p. 2262.1) in women.[1-7] It should be noted that finasteride should not be used in women who are or may become pregnant (see Precautions, below).

1. Falsetti L, *et al.* Comparison of finasteride versus flutamide in the treatment of hirsutism. *Eur J Endocrinol* 1999; 141: 361–7.
2. Moghetti P, *et al.* Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000; 85: 89–94.
3. Müderris II, *et al.* A prospective, randomized trial comparing flutamide (250 mg/d) and finasteride (5 mg/d) in the treatment of hirsutism. *Fertil Steril* 2000; 73: 984–7.
4. Bayram F, *et al.* Comparison of high-dose finasteride (5 mg/day) versus low-dose finasteride (2.5 mg/day) in the treatment of hirsutism. *Eur J Endocrinol* 2002; 147: 467–71.
5. Luzzachi F, Rondinone R. Use of cyproterone acetate, finasteride, and spironolactone to treat idiopathic hirsutism. *Fertil Steril* 2003; 79: 942–6.
6. Beigi A, *et al.* Finasteride versus cyproterone acetate-estrogen regimens in the treatment of hirsutism. *Int J Gynaecol Obstet* 2004; 87: 29–33.
7. Tartagni M, *et al.* Intermittent low-dose finasteride is as effective as daily administration for the treatment of hirsute women. *Fertil Steril* 2004; 82: 752–5.

Malignant neoplasms of the prostate. Finasteride appears to have little effect in established prostate cancer,[1,2] but is under investigation for its prevention (p. 712.3), and guidelines for such use have been issued.[3] The results of 1 small study[4] of its effects on the prostate found little evidence to support its use for prevention of malignancy in patients at high risk. In healthy men, a large controlled study, the Prostate Cancer Prevention Trial (PCPT),[5] found that 7 years of finasteride prophylaxis reduced the incidence of prostate cancer by about 25% compared with placebo, but this benefit was offset by an increased risk of high-grade tumours associated with finasteride. The risk-benefit implications of these results have been debated, although some commentaries[6-9] suggest that preventive use would be justified, at least in selected patients. Further analysis[10] of the PCPT data found that finasteride had introduced a detection bias for both prostate cancer and for high-grade prostate cancer. Finasteride increased the sensitivity of prostate specific antigen (PSA) testing, implying that the PCPT primary findings of increased risk of high-grade tumours were due, at least in part, to improved detection. The reported 25% decrease in prostate cancer incidence was also likely to be an underestimate. The European Association of Urology has endorsed a recommendation that prostate cancer management guidelines be updated to reflect these findings.[11]

1. Presti JC, *et al.* Multicenter, randomized, double-blind placebo controlled study to investigate the effect of finasteride (MK-906) on stage D prostate cancer. *J Urol (Baltimore)* 1992; 148: 1201–4.
2. Rittmaster RS. Finasteride. *N Engl J Med* 1994; 330: 120–5.
3. Kramer BS, *et al.* American Society of Clinical Oncology Health Services Committee, American Urological Association Practice Guidelines Committee. Use of 5-α-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Clin Oncol* 2009; 27: 1502–16. Correction. *ibid.*; 2742. Also available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2668556/pdf/zlj1502.pdf (accessed 16/06/10)
4. Cote RJ, *et al.* The effect of finasteride on the prostate gland in men with elevated serum prostate-specific antigen levels. *Br J Cancer* 1998; 78: 413–18.
5. Thompson IM, *et al.* The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; 349: 215–24.
6. Parnes HL, *et al.* Prevention of hormone-related cancers: prostate cancer. *J Clin Oncol* 2005; 23: 368–77.
7. Unger JM, *et al.* Estimated impact of the Prostate Cancer Prevention Trial on population mortality. *Cancer* 2005; 103: 1375–80.
8. Lotan Y, *et al.* Implications of the prostate cancer prevention trial: a decision analysis model of survival outcomes. *J Clin Oncol* 2005; 23: 1911–20.
9. Vickers AJ, *et al.* Finasteride to prevent prostate cancer: should all men or only a high-risk subgroup be treated? *J Clin Oncol* 2010; 28: 1112–16.
10. Thompson IM, *et al.* Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* 2006; 98: 1128–33.
11. Teillac P, Abrahamsson P-A. The Prostate Cancer Prevention Trial and its implications for clinical practice: a european consensus. *Eur Urol Suppl* 2006; 5: 640–6.

Adverse Effects

The most commonly reported adverse effects of finasteride are decreased libido, erectile dysfunction, ejaculation disorders, and reduced volume of ejaculate.

Breast tenderness and enlargement (gynaecomastia) may occur, and there have been reports of hypersensitivity reactions such as swelling of the lips and face, pruritus, urticaria, and rashes. Testicular pain has also been reported.

Incidence of adverse effects. In a study using prescription event monitoring data,[1] the most commonly reported adverse effects of finasteride in 14 772 patients were impotence or ejaculatory failure (2.1% of patients), reduced libido (1%), and breast disorders such as gynaecomastia (0.4%). Adverse effects reported in a single patient each, and verified on rechallenge, were exfoliative dermatitis, perioral numbness, and swollen glands. Finasteride appeared to be associated with ataxia in 1 patient and wheeziness in another.

1. Wilton L, *et al.* The safety of finasteride used in benign prostatic hypertrophy: a non-interventional observational cohort study in 14 772 patients. *Br J Urol* 1996; 78: 379–84.

Effects on the breast. Gynaecomastia was the adverse effect of finasteride most frequently reported to the FDA between June 1992 and February 1995 (a total of 214 reports).[1] The onset after therapy ranged from 14 days to 2.5 years, and the condition could be unilateral or bilateral. Mastectomy was performed in 12 men. Of the 86 men for whom follow-up information was available, partial or complete remission of gynaecomastia occurred in 80%, and no change occurred in 20%. In 2 of the cases, primary intraductal breast carcinoma was subsequently found, although 1 probably had breast cancer before finasteride therapy.

A subsequent review by the MHRA[2] reported 53 cases of male breast cancer associated with the use of finasteride worldwide; most cases occurred within 5 years of starting treatment. There was a trend towards male breast cancer occurring more frequently with finasteride compared with placebo in clinical studies, although the overall incidence was not significantly different. There have also been 4 reports of breast cancer in women after unlicensed use of finasteride; cases occurred after relatively shorter periods of treatment (up to 1 year). Patients were advised to promptly report any changes in their breast tissue during finasteride treatment, such as lumps, pain, or nipple discharge. However, there was no strong evidence to suggest that gynaecomastia was a precursor to breast cancer as it occurs in only 9% of breast cancer cases, but has been reported in up to 50% of men in the general population.

1. Green L, *et al.* Gynecomastia and breast cancer during finasteride therapy. *N Engl J Med* 1996; 335: 823.
2. MHRA. MHRA public assessment report: the risk of male breast cancer with finasteride (issued December 2009). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con06 (accessed 23/03/10)

Effects on mental function. Depression has been reported[1,2] in 20 patients given finasteride for the treatment of alopecia. In most cases the depression began about 3 to 4 months after starting finasteride, and resolved within a few weeks of stopping it. In 2 patients rechallenged with finasteride, depression recurred within 2 weeks of restarting the drug.[1]

1. Altomare G, Capella GL. Depression circumstantially related to the administration of finasteride for androgenetic alopecia. *J Dermatol* 2002; 29: 665–9.
2. Health Canada. Finasteride: suspected association with depression. *Can Adverse React News* 2004; 14 (1): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n1-eng.pdf (accessed 02/09/08)

Precautions

Finasteride should be used with caution in hepatic impairment. When used for benign prostatic hyperplasia, finasteride should be used with caution in men at risk of obstructive uropathy. Patients should be evaluated for prostatic carcinoma before and during therapy. Use of finasteride decreases concentrations of serum markers of prostate cancer such as prostate specific antigen (PSA) by up to 50% even when cancer is present, and reference values should be adjusted accordingly; the ratio of free to total PSA (percent free PSA) remains constant.

Studies in *animals* suggest finasteride could produce feminisation (hypospadia) of a male fetus if used in pregnant women; therefore, its use is contra-indicated in women who are or may become pregnant. In addition, it is recommended that women in this category should not handle crushed or broken finasteride tablets. Finasteride has been detected in semen, therefore use of a condom is recommended if the patient's sexual partner is, or may become, pregnant.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies finasteride 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)

Pharmacokinetics

Finasteride is absorbed after oral doses, and peak plasma concentrations occur in 1 to 2 hours. The mean bioavailability has variously been reported as 63% and 80%. It is about 90% bound to plasma protein. Finasteride crosses the blood-brain barrier, and is distributed into semen. It is metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP3A4, and excreted in urine and faeces as metabolites. The mean terminal half-life is about 6 hours in patients under 60 years of age but may be prolonged to about 8 hours in those 70 years of age or older.

References.

1. Steiner JF. Clinical pharmacokinetics and pharmacodynamics of finasteride. *Clin Pharmacokinet* 1996; 30: 16–27.
2. Suzuki R, *et al.* Saturable binding of finasteride to steroid 5α-reductase as determinant of nonlinear pharmacokinetics. *Drug Metab Pharmacokinet* 2010; 25: 208–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Andropel; Avertex; Capilfor; Daric; Finasterin; Finprostat; Finterac; Flutiamik; Folcres; HPB; Ivix Fin; Nasteril; Propecia; Proscar; Prosmin; Prostanil; Prostanovag; Prostene; Q-Prost Alopex; Q-Prost; Renacidin; Ridefin; Surrico; Tealep; Tresaride; Tricofarma; Urofin; Urototal; Vetiprost; *Austral.*: Finasta; Finnacar; Propecia; Proscar; *Austria*: Androfin; Propecia; Proscar; *Belg.*: Proscar; *Braz.*: Alfasin; Capyla; Fendical; Finalop; Finapecia; Finarid; Finastec; Finastil; Flaxin; Nasterid A; Nasterid; Pracap†; Pronasteron; Propecia; Proscar; Prostide; *Canad.*: Propecia; Proscar; *Chile*: Folipil; Prohair; Proscar; Regener; Saniprostol; Tricoplus; Vastus; *China*:

The symbol † denotes a preparation no longer actively marketed

Ai Shi Lie (艾仕列); Bao Li An (葆利安); Duo Shai (多晒); Finatra (如川); Pu Lie (孚列); He Shu (合舒); Ji You (吉优); Jun Neng (俊能); Ka Bo (卡波); Kang Lie Su (康列苏); Kui An (奎安); Lan Le (蓝乐); Li Er Quan (利尔泉); Lie Qin (列沁); Lishu (莉舒); LiTong (立同); Long Tong (隆通); Propecia (保法止); Proscar (保列治); Pu Lie An (浦列安); Pu Luo Ping (普洛平); Qian Li Xin (前力欣); Qian Nuo Lin (千诺林); Shi Yi (士怡); Si Jun Yi (司君宜); Tian Shu Xin (恬舒新); Xian Li Xiao (先立晓); Xing Bao (星保); Yi An Lin (意安林); Yi Ru Te (易如特); Yi Shu Sheng (逸舒升); Yi Tong (亦通); Yi You Rui Xin (易优瑞欣); Zai An Lie (再安列); *Cz.*: Androfin; Apo-Finas; Duromeran†; Edufil†; Finajelf; Finanorm; Finard; Finex; Finpros; Gefin; Hyplafin; Ibition†; Lekoprost; Mostrafin; Penester; Propecia; Proscar†; Radicut†; ***Denm.***: Finaprost; Finastad; Propecia; Proscar; ***Fin.***: Gefina; Propecia; Proscar; Tifisterid; ***Fr.***: Chibro-Proscar; Propecia; ***Ger.***: FinaHAIR†; Finamed; Finapil; Finascar; Finural; Propecia; Proscar; Prosmin; ***Gr.***: Alsteride; Avielid; Finaprost; Finar; Finastir; Finazil; Finescar; Fisterid; Glopisine; Pervil; Poruxin; Profin; Profinosa; Prohype; Propecia; Proplasia; Proscar; Prostafin; ***Hong Kong***: Fincar; Propecia; Proscar; ***Hung.***: Andofin; Finanorm; Finastep; Finpros; Hyplafin; Proscar; Prosterid; Sterakfin; ***India***: Finabald; Finalo; Finara; Finaride; Finast; Finastat; Finax; Fincar; Finpecia; Finster; Fintride; Fistide; Monast; ***Indon.***: Alopros; Finaxal†; Finpro; Proscar; Prostacom; Prostide; Reprostom; ***Irl.***: Finocar; Fintex; Fintrid; Profal; Proscar; ***Israel***: Pro-Cure; Propecia; ***Ital.***: Finastid; Folians; Genaprost; Pilus; Propecia; Proscar; Prostide; ***Malaysia***: Propecia; Proscar; ***Mex.***: Borealist; Fhilterin; Propeshia; Proscar; Riterid-Z; Syndrex; Tealep; Teriurin; Vanorid; ***Neth.***: Finagalen†; Finahold†; Finajelf†; Finaschwarz†; Finastad†; Propecia; Proscar; ***Norw.***: Proscar; ***NZ***: Finaccord; Fintral; Propecia; Proscar; ***Philipp.***: Atepros; Finarid; Finast; Pronax; Propecia; Proscar; Prostab; Prostanus; Prosteride; ***Pol.***: Ambulase†; Antiprost; Apo-Fina; Aprost; FinaGen; Finamef; Finanorm; Finaran; Finaride; Finaster; Finpros; Fintral; Finxta; Hyplafin; Lifin; Penester; Propecia; Proscar; Symasteride; Ulgafen; Zasterid; ***Port.***: Binpros†; Finox; Growancer†; Propecia; Proscar; Prostacide†; Prostafin; Zidoril†; Zylfina†; ***Rus.***: Alfinal (Альфинал); Finast (Финаст); Finpros (Финпрос); Penester (Пенестер); Proscar (Проскар); Prosterid (Простерид); Zerlon (Зерлон); ***S.Afr.***: Fincar; Finpecia; Finpro; Propecia; Proscar; ***Singapore***: Finas; Finast; Propecia; Proscar; ***Spain***: Alocare; Arahormo; Ativol†; Eucoprost†; Lambdaxel; Litace; Maxpil; Normomale; Propecia; Proscar; ***Swed.***: Propecia; Proscar; ***Switz.***: Alocapil; Finacapil; Finasterax; Propecia; Proscar; ***Thai.***: Firide; Harifin; Propecia; Proscar; Prosteride; Stercia; Sterzar; ***Turk.***: Alofin; Dilaprost; Finarid; Propecia; Proscar; Prosterit; ***UK***: Propecia; Proscar; ***Ukr.***: Adenosterid (Аденостерид-Здоровье); Finast (Финаст)†; Penester (Пенестер); Prosterid (Простерид)†; ***USA***: Propecia; Proscar; ***Venez.***: Nasterol; Propecia; Proscar; Prosdina.

Multi-ingredient Preparations. *Arg.*: Prosdox Duo; ***Hung.***: Alfin Combo; Duamild; ***India***: Contiflo-OD-F; Finabald-T; Finast T; Flokind-F; Geriflo; Urimax F; ***Mex.***: Profidox.

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

Flavoxate Hydrochloride

(BANM, USAN, rINNM)

DW-61; Flavoksat Hidroklorür; Flavoxate, Chlorhydrate de; Flavoxathydrochlorid; Flavoxati hydrochloridum; Flavoxato, hidrocloruro de; Hidrocloruro de flavoxato; NSC-114649; Rec-7-0040; Флавоксата Гидрохлорид.

2-Piperidinoethyl 3-methyl-4-oxo-2-phenyl-4*H*-chromene-8-carboxylate hydrochloride.

$C_{24}H_{25}NO_4HCl$=427.9

CAS — 15301-69-6 (flavoxate); 3717-88-2 (flavoxate hydrochloride).

ATC — G04BD02.

ATC Vet — QG04BD02.

UNII — 9C05J6089W.

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

Ph. Eur. 8: (Flavoxate Hydrochloride). A white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Flavoxate Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water, in alcohol, and in dichloromethane. Protect from light.

Uses and Administration

Flavoxate hydrochloride is described as a smooth muscle relaxant but it also has antimuscarinic actions (see, p. 1310.3); it is a tertiary amine. It is used for the symptomatic relief of pain, urinary frequency, and incontinence associated with inflammatory disorders of the urinary tract. It is also used for the relief of vesicourethral spasms resulting from instrumentation or surgery. A usual dose is 200 mg orally three times daily.

Urinary incontinence. Flavoxate is indicated mainly in the treatment of urge incontinence (p. 2349.2). Results of studies have sometimes been disappointing,[1,2] although adverse effects are said to be less marked than those seen with other antimuscarinics such as oxybutynin.[3] In the UK, guidelines issued by NICE suggest that flavoxate should not be recommended for the treatment of urinary incontinence or overactive bladder in women; other antimuscarinics are preferred.[4]

1. Chapple CR. *et al.* Double-blind, placebo-controlled, cross-over study of flavoxate in the treatment of idiopathic detrusor instability. *Br J Urol* 1990; **66**: 491–4.
2. Dahm TL. *et al.* Flavoxate treatment of micturition disorders accompanying benign prostatic hypertrophy: a double-blind placebo-controlled multicenter investigation. *Urol Int* 1995; **55**: 205–8.
3. Fehrmann-Zumpe P. *et al.* Using flavoxate as primary medication for patients suffering from urge symptomatology. *Int Urogynecol J* 1999; **10**: 91–5.
4. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Ocular effects, including increased intra-ocular pressure, are occasionally troublesome. Other adverse effects include sedation or fatigue, vertigo, and hypersensitivity reactions. Leucopenia or eosinophilia has been reported rarely.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Flavoxate is readily absorbed from the gastrointestinal tract and rapidly metabolised, about 50 to 60% of a dose being excreted in the urine within 24 hours as methyl flavone carboxylic acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bladuril; ***Belg.***: Urispas; ***Braz.***: Genurin-S; ***Canad.***: Urispas; ***Chile***: Bladuril; Urodial; ***China***: Bei Si Qing (贝斯清); Chang Er Da (畅尔达); Du Luo Jie (渡洛捷); Genurin (津源灵); Ji Shi Da (吉时达); Luo Ao Ke (洛沃克); Soolda (舒尔达); You Bi Da (优必达); ***Denm.***: Urispadol; ***Fr.***: Urispas; ***Ger.***: Spasuret†; ***Gr.***: Verispasmin; ***Hong Kong***: Urispas; ***India***: Favate; Flavate; Flavoride; Flavospas; Urisol; Urispas; ***Indon.***: Uroxal; ***Irl.***: Urispas; ***Ital.***: Genurin; ***Jpn***: Bladeron; Lady Guard†; ***Malaysia***: Cleanxate; Uripax; Urispas; ***Mex.***: Bladuril; ***Neth.***: Urispas; Uronid†; ***Port.***: Urispas; ***S.Afr.***: Urispas; ***Singapore***: Cleanxate; Genurin; Lavoxen; Urispas; ***Spain***: Uronid; ***Switz.***: Urispas; ***Thai.***: Flavo-Spa; Flavorin; Spasdic; Spasuri; U-Spa; Urispas; Uroxate; Voxate; ***Turk.***: Urispas; ***UK***: Urispas; ***USA***: Urispas; ***Venez.***: Genurin.

Multi-ingredient Preparations. *Arg.*: Algio-Bladuril; ***Ital.***: Cistalgan.

Pharmacopoeial Preparations
BP 2014: Flavoxate Tablets;
USP 36: Flavoxate Hydrochloride Tablets.

Imidafenacin *(rINN)*

Imidafenacina; Imidafénacine; Imidafenacinum; KRP-197; KRP-1979; Ono-8025; Имидафенацин.

4-(2-Methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide.

$C_{20}H_{21}N_3O$=319.4

CAS — 170105-16-5.

UNII — XJR8Y07LJO.

Profile

Imidafenacin is an antimuscarinic that is used in the treatment of urinary frequency, urgency, and incontinence (p. 2349.2). It is given in an oral dose of 100 micrograms twice daily, after food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Staybla; Uritos.

Lodenafil Carbonate *(rINN)*

Carbonato de Lodenafilo; Lodénafil Carbonate; Lodenafili Carbonas; Лоденафиль Карбонат.

Bis[2-(4-[4-ethoxy-3-(1-methyl-7-oxo-3-propyl-4,7-dihydro-1*H*-pyrazolo(4,3-*d*)pyrimidin-5-yl]phenylsulfonyl)piperazin-1-yl)ethyl]carbonate.

$C_{47}H_{62}N_{12}O_{11}S_2$=1035.2

CAS — 398507-55-6.

Profile

Lodenafil carbonate is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2); it is used orally in the management of erectile dysfunction (p. 2348.2). A suggested dose is 80 mg taken 20 minutes to 1 hour before sexual intercourse.

References.
1. Glina S. *et al.* Efficacy and tolerability of lodenafil carbonate for oral therapy in erectile dysfunction: a phase II clinical trial. *J Sex Med* 2009; **6**: 553–7.
2. Glina S. *et al.* Efficacy and tolerability of lodenafil carbonate for oral therapy of erectile dysfunction: a phase III clinical trial. *J Sex Med* 2010; **7**: 1928–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Helleva.

Mirabegron *(USAN, rINN)*

Mirabegrón; Mirabégron; Mirabegronum; YM-178; Мирабегрон.

2-(2-Amino-1,3-thiazol-4-yl)-*N*-[4-(2-[[(2*R*)-2-hydroxy-2-phenylethyl]amino]ethyl)phenyl]acetamide.

$C_{21}H_{24}N_4O_2S$=396.5

CAS — 223673-61-8.

ATC — G04BD12.

ATC Vet — QG04BD12.

UNII — MVR3JL3B2V.

Uses and Administration

Mirabegron is a beta$_3$-adrenoceptor agonist used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome (p. 2349.2). The usual oral dose is 25 to 50 mg once daily, which is usually effective within 8 weeks.

For doses in hepatic and renal impairment, see below.

References.
1. Gras J. Mirabegron for the treatment of overactive bladder. *Drugs Today* 2012; **48**: 25–32.
2. Bhide AA. *et al.* Use of mirabegron in treating overactive bladder. *Int Urogynecol J* 2012; **23**: 1345–8.

Administration in hepatic impairment. Licensed product information states that the oral dose of mirabegron should not exceed 25 mg once daily in patients with moderate hepatic impairment (Child-Pugh class B), and its use is not recommended in those with severe impairment (Child-Pugh class C) due to a lack of data; no dose adjustment is necessary in mild impairment (Child-Pugh class A).

It is also recommended that the dose of mirabegron is reduced in patients with hepatic impairment who are also taking strong inhibitors of cytochrome P450 isoenzyme CYP3A. In patients with mild hepatic impairment, a maximum dose of 25 mg daily may be given; co-administration is not recommended in patients with more severe hepatic impairment.

Administration in renal impairment. Licensed product information states that the oral dose of mirabegron should not exceed 25 mg once daily in patients with severe renal impairment (creatinine clearance [CC] 15 to 29 mL/minute), and its use is not recommended in those with end-stage renal disease (CC less than 15 mL/minute), or requiring haemodialysis, due to a lack of data; no dose adjustment is necessary in mild or moderate impairment (CC 30 to 89 mL/minute).

It is also recommended that the dose of mirabegron is reduced in patients with renal impairment who are also taking strong inhibitors of cytochrome P450 isoenzyme CYP3A. In patients with mild or moderate renal impairment a maximum dose of 25 mg daily of mirabegron may be used; co-administration is not recommended in patients with severe renal impairment.

Adverse Effects and Precautions

The most commonly reported adverse effects with mirabegron are hypertension, nasopharyngitis, urinary-tract infection, and headache. Other frequently reported adverse effects include nausea, diarrhoea, constipation, dizziness, tachycardia, and dry mouth.

Mirabegron is not recommended in patients with severe uncontrolled hypertension and blood pressure should be monitored in all patients, particularly those with hypertension. It should be used with caution in those with hepatic or renal impairment. Due to the risk of urinary retention, mirabegron should be given with caution to patients with clinically significant bladder outlet obstruction or those who are also taking antimuscarinics for the treatment of overactive bladder syndrome.

References.
1. Tyagi P. *et al.* Mirabegron: a safety review. *Expert Opin Drug Safety* 2011; **10**: 287–94.

Interactions

Strong inhibitors of cytochrome P450 CYP3A isoenzymes may increase mirabegron exposure, and a lower dose of mirabegron is recommended during concomitant therapy in patients with hepatic or renal impairment (see p. 2360.3).

Mirabegron is a moderate inhibitor of the cytochrome P450 isoenzyme CYP2D6 and concomitant use with substrates such as desipramine and metoprolol increases systemic exposure to these drugs. When used with mirabegron, appropriate monitoring and dose adjustment of CYP2D6 substrates may be necessary, particularly those with a narrow therapeutic index such as flecainide, propafenone, and thioridazine.

For the effect of mirabegron on digoxin, see p. 1358.1.

Pharmacokinetics

After oral doses of mirabegron, peak plasma concentrations occur in about 3.5 hours. It is about 71% bound to plasma proteins and widely distributed in the body. Mirabegron is metabolised via multiple pathways involving butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), and possibly alcohol dehydrogenase in addition to cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Two major inactive metabolites are excreted in the urine and the faeces; about 25% of a dose is excreted unchanged in the urine. The terminal elimination half-life is about 50 hours. It has been detected in the milk of *rats*.

References.
1. Blink C, *et al.* Single dose pharmacokinetics and absolute bioavailability of mirabegron, a β 3-adrenoceptor agonist for treatment of overactive bladder. *Int J Clin Pharmacol Ther* 2012; **50**: 838–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Betanis; *UK*: Betmiga; *USA*: Myrbetriq.

Naftopidil *(rINN)*

BM-15275; KT-611; Naftopidilum; Нафтопидил.
(±)-4-(*o*-Methoxyphenyl)-α-[(1-naphthyloxy)methyl]-1-piperazineethanol.
$C_{24}H_{28}N_2O_3$=392.5
CAS — 57149-07-2.
UNII — R9PHW595FN.

Profile

Naftopidil is a peripheral alpha$_1$-adrenoceptor blocker that is structurally related to urapidil (p. 1520.2) and has similar general properties. It is used in benign prostatic hyperplasia to relieve symptoms of urinary obstruction.

References.
1. Yokoyama T, *et al.* Comparison of 25 and 75 mg/day naftopidil for lower urinary tract symptoms associated with benign prostatic hyperplasia: a prospective, randomized controlled study. *Int J Urol* 2006; **13**: 932–8.
2. Maruyama O, *et al.* Naftopidil monotherapy vs naftopidil and an anticholinergic agent combined therapy for storage symptoms associated with benign prostatic hyperplasia: a prospective randomized controlled study. *Int J Urol* 2006; **13**: 1280–5.
3. Masumori N, *et al.* Short-term efficacy and long-term compliance/treatment failure of the α 1 blocker naftopidil for patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Scand J Urol Nephrol* 2007; **41**: 422–9.
4. Oh-oka H. Effect of naftopidil on nocturia after failure of tamsulosin. *Urology* 2008; **72**: 1051–5.
5. Ukimura O, *et al.* Naftopidil versus tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia with special reference to the storage symptom: a prospective randomized controlled study. *Int J Urol* 2008; **15**: 1049–54.
6. Garimella PS, *et al.* Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2009 (accessed 23/03/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: DiShuang (帝爽); Bapidil (博帝); Ge Rui Jia (格瑞佳); Jun Lie Xin (君列欣); Kun Da (坤达); Lai Luo Er (来络尔); Na Tuo (那妥); Pu Chang (浦畅); Shu Er (疏尔); Sitandi (司坦迪); Yu Chang (愈畅); Zai Chang (再畅); *Jpn*: Avishot†; Flivas.

Oxendolone *(USAN, rINN)*

Oxendolona; Oxendolonum; TSAA-291; Оксендолон.
16β-Ethyl-17β-hydroxyestr-4-en-3-one.
$C_{20}H_{30}O_2$=302.5
CAS — 33765-68-3.
UNII — MN4I850D4P.

Profile

Oxendolone is an anti-androgen that has been used in the treatment of benign prostatic hyperplasia.

Oxybutynin *(BAN, USAN, rINN)*

Oxibutinina; Oxybutynine; Oxybutyninum; Оксибутинин.
4-Diethylaminobut-2-ynyl 2-cyclohexyl-2-phenylglycolate; 4-(Diethylamino)-2-butynyl α-phenylcyclohexaneglycolic acid ester.
$C_{22}H_{31}NO_3$=357.5
CAS — 5633-20-5.
ATC — G04BD04.
ATC Vet — QG04BD04.
UNII — K9P6MC7092.

Oxybutynin Hydrochloride *(BANM, rINNM)*

5058; Hidrocloruro de oxibutinina; MJ-4309-1; Oksibütinin Hidroklorür; Oksibutinino hidrochloridas; Oksibutyniinihydrokloridi; Oksybutyniny chlorowodorek; Oxibutinina, hidrocloruro de; Oxibutinin-hidroklorid; Oxibutyninhydroklorid; Oxybutynin Chloride (USAN); Oxybutynin hydrochlorid; Oxybutynine, chlorhydrate d'; Oxybutyninhydrochlorid; Oxybutynini Hydrochloridum; Оксибутинина Гидрохлорид.
4-Diethylaminobut-2-ynyl α-cyclohexylmandelate hydrochloride; 4-(Diethylamino)but-2-ynyl (*RS*)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride.
$C_{22}H_{31}NO_3$,HCl=394.0
CAS — 1508-65-2.
ATC — G04BD04.
ATC Vet — QG04BD04.
UNII — L9F3D9RENQ.

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

Ph. Eur. 8: (Oxybutynin Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; practically insoluble in cyclohexane. Protect from light.

USP 36: (Oxybutynin Chloride). A white, practically odourless, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; very soluble in chloroform and in methyl alcohol; slightly soluble in ether; very slightly soluble in hexane.

Uses and Administration

Oxybutynin hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p. 1310.3); it also has direct effects on smooth muscle. It is used for the management of urinary frequency, urgency, and incontinence in neurogenic bladder disorders and in idiopathic detrusor instability, and as an adjunct to nonpharmacological therapy for nocturnal enuresis.

Usual oral doses of oxybutynin hydrochloride are 5 mg two or three times daily, increased to 5 mg four times daily if required. In elderly patients lower doses of 2.5 or 3 mg twice daily initially, increased to 5 mg twice daily if necessary, may be adequate. Modified-release preparations of oxybutynin hydrochloride are also available. The initial dose is 5 mg once daily, increased by 5 mg at weekly intervals if necessary, up to a maximum of 20 or 30 mg daily, depending on the preparation.

Oxybutynin is also used topically. A transdermal patch is available that supplies 3.9 mg of oxybutynin daily. The patch should be applied to intact skin on the abdomen, hip, or buttocks and replaced every 3 to 4 days; re-application to the same site should be avoided for 7 days. Alternatively, oxybutynin can be applied as a gel in the management of overactive bladder syndrome; dosage depends on the brand used. *Gelnique* 10% gel (*Watson, USA*) contains 100 mg of oxybutynin hydrochloride in each sachet; the contents of one sachet is applied once daily to intact skin on the abdomen, thighs, upper arms, or shoulders. *Anturol* 3% gel (*Antares, USA*) delivers 28 mg of oxybutynin in each pump actuation; 3 actuations should be applied once daily to intact skin as for the sachet preparation.

For doses in children, see below.

Administration in children. Oxybutynin hydrochloride is licensed in the UK and USA for **neurogenic bladder disorders** in children. Additionally, in the UK, oxybutynin is also licensed for the treatment of **idiopathic overactive bladder** and **nocturnal enuresis**.

For these indications, children aged from over 5 to 12 years of age may be given the following doses:

- the *conventional oral formulation* may be given in an initial dose of 2.5 to 3 mg twice daily, increased to 5 mg twice or three times daily according to response; for nocturnal enuresis, the last dose should be given before bedtime
- as a *modified-release tablet* the initial dose is 5 mg once daily, increased by 5-mg increments at weekly intervals to a maximum daily dose of 15 or 20 mg, depending on the preparation, and according to response. Modified-release preparations are not recommended for children who are unable to swallow the tablet whole

In addition, for the treatment of idiopathic overactive bladder or neurogenic bladder disorders, the *BNFC* suggests that children aged 2 to 5 years may be given a dose of 1.25 to 2.5 mg as a *conventional oral formulation* 2 or 3 times daily.

Children from 12 years of age may be given adult doses (see Uses and Administration, above).

Oxybutynin may also be given by *intravesical instillation*, although unlicensed by this route. The *BNFC* suggests a dose of 5 mg (as the hydrochloride) in 30 mL of solution, 2 or 3 times daily, in children aged 2 to 18 years.

Benign prostatic hyperplasia. Although there have been concerns about the use of antimuscarinics in patients with symptomatic benign prostatic hyperplasia (p. 2347.1) some patients have lower urinary tract symptoms suggestive of overactive bladder, and antimuscarinics such as oxybutynin are increasingly being used for treatment, either alone or as adjuncts. In men who had incomplete relief of urinary storage symptoms (such as frequency, nocturia, and urge incontinence) with tamsulosin alone, addition of a prolonged-release formulation of oxybutynin gave further symptom relief compared with placebo.[1]

1. MacDiarmid SA, *et al.* Efficacy and safety of extended-release oxybutynin in combination with tamsulosin for treatment of lower urinary tract symptoms in men: randomized, double-blind, placebo-controlled study. *Mayo Clin Proc* 2008; **83**: 1002–10.

Nocturnal enuresis. Antimuscarinics such as oxybutynin reduce uninhibited bladder contractions but, although they may be of use in diurnal enuresis, they are rarely of benefit in nocturnal enuresis (p. 2349.1) alone. Oxybutynin did not appear to be effective in treating primary nocturnal enuresis in children with normal bladders.[1] However, children with low bladder capacity and detrusor instability may derive some benefit from oxybutynin.[2,3]

1. Lovering JS, *et al.* Oxybutynin efficacy in the treatment of primary enuresis. *Pediatrics* 1988; **82**: 104–6.
2. Kosar A, *et al.* Effectiveness of oxybutynin hydrochloride in the treatment of enuresis nocturna: a clinical and urodynamic study. *Scand J Urol Nephrol* 1999; **33**: 115–18.
3. Nevéus T. Oxybutynin, desmopressin and enuresis. *J Urol (Baltimore)* 2001; **166**: 2459–62.

Urinary incontinence. In addition to its antimuscarinic effect, oxybutynin has a direct antispasmodic effect which helps reduce the number of uninhibited bladder contractions in urge incontinence (see p. 2349.2). It is effective when given orally[1-4] or via a transdermal patch.[5-7] NICE considers conventional oral oxybutynin formulations to be the drug of first choice in women with overactive bladder syndrome or mixed incontinence if bladder training has been ineffective.[8] However, adverse effects may limit its use; if immediate-release oxybutynin is not well tolerated, a controlled-release or transdermal formulation may be considered as an alternative.[8] The comparative pharmacokinetics and efficacy of the different formulations have been reviewed;[9] there is some evidence that transdermal formulations may be better tolerated in the elderly, although direct comparative studies are mostly lacking.

Oral oxybutynin can be useful in the management of neurogenic detrusor hyperreflexia in adults[10,11] and children.[12] Direct instillation of oxybutynin into the bladder has also been tried. In one study[13] that included patients aged 1 to 34 years, 21 out of 32 patients became totally continent using an intravesical dose of 300 micrograms/kg daily, given in 3 divided doses. A further 7 patients became continent with doses titrated up to a maximum of 900 micrograms/kg daily, but another 4 remained incontinent. Other reports[14,15] have used single or multiple doses of 5 mg, often prepared by dispersing a crushed 5-mg tablet in 30 mL of distilled water or sodium chloride 0.9%.

1. Riva D, Casolati E. Oxybutynin chloride in the treatment of female idiopathic bladder instability: results from double blind treatment. *Clin Exp Obstet Gynecol* 1984; **11**: 37–42.
2. Moore KH, *et al.* Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. *Br J Urol* 1990; **66**: 479–85.
3. Tapp AJS, *et al.* The treatment of detrusor instability in postmenopausal women with oxybutynin chloride: a double blind placebo controlled study. *Br J Obstet Gynaecol* 1990; **97**: 521–6.
4. Siddiqui MA, *et al.* Oxybutynin extended-release: a review of its use in the management of overactive bladder. *Drugs* 2004; **64**: 885–912.
5. Davila GW, *et al.* A short-term, multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *J Urol (Baltimore)* 2001; **166**: 140–5.
6. Dmochowski RR, *et al.* Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *J Urol (Baltimore)* 2002; **168**: 580–6.
7. Dmochowski RR, *et al.* Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology* 2003; **62**: 237–42.
8. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

The symbol † denotes a preparation no longer actively marketed

9. Kennelly MJ. A comparative review of oxybutynin chloride formulations: pharmacokinetics and therapeutic efficacy in overactive bladder. *Rev Urol* 2010; 12: 12–19.
10. O'Leary M, *et al.* Effect of controlled-release oxybutynin on neurogenic bladder function in spinal cord injury. *J Spinal Cord Med* 2003; 26: 159–62.
11. Bennett N, *et al.* Can higher doses of oxybutynin improve efficacy in neurogenic bladder? *J Urol (Baltimore)* 2004; 171: 749–51.
12. Franco I, *et al.* Efficacy and safety of oxybutynin in children with detrusor hyperreflexia secondary to neurogenic bladder dysfunction. *J Urol (Baltimore)* 2005; 173: 221–5.
13. Haferkamp A, *et al.* Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. *Spinal Cord* 2000; 38: 250–4.
14. Szollar SM, Lee SM. Intravesical oxybutynin for spinal cord injury patients. *Spinal Cord* 1996; 34: 284–7.
15. Lose G, Nørgaard JP. Intravesical oxybutynin for treating incontinence resulting from an overactive detrusor. *BJU Int* 2001; 87: 767–73.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2.

Animal studies have shown reproductive toxicity with high doses of oxybutynin, hence the recommendation that it should be avoided during pregnancy; caution should also be observed during breast feeding.

Effects on body temperature. A 76-year-old man taking oxybutynin hydrochloride 5 mg three times daily suffered heatstroke on a day when the ambient temperature was about 37 degrees. He had had a similar febrile episode the previous summer while taking oxybutynin.[1]

1. Adubofour KO, *et al.* Oxybutynin-induced heatstroke in an elderly patient. *Ann Pharmacother* 1996; 30: 144–7.

Effects on the eyes. After 4 weeks of treatment, the adverse ocular effects of oxybutynin and tolterodine were evaluated in 24 and 28 women, respectively, being treated for urge incontinence.[1] The incidence of adverse effects reported by the patients was similar for the 2 drugs. A burning sensation in the eyes occurred in about half the women, but reports of a foreign-body sensation and dry eyes were less frequent. There was a reduction in accommodation amplitude although this was statistically significant only for oxybutynin, and pupillary diameter in dim light was only significantly larger for tolterodine. Tear film stability was found to be reduced for both drugs, but intraocular pressure was not significantly affected.

Acute angle-closure glaucoma has been reported in an elderly woman taking oxybutynin for urge incontinence.[2]

1. Altan-Yaycioglu R, *et al.* Ocular side-effects of tolterodine and oxybutynin, a single-blind prospective randomized trial. *Br J Clin Pharmacol* 2005; 59: 588–92.
2. Sung VCT, Corridan PG. Acute-angle closure glaucoma as a side-effect of oxybutynin. *Br J Urol* 1998; 81: 634–5.

Effects on the gastrointestinal tract. Reflux oesophagitis has been reported[1] in a 36-year-old woman with cerebral palsy and hiatus hernia who had taken oxybutynin for 5 years to prevent urinary incontinence. Symptoms of gastro-oesophageal reflux resolved when oxybutynin was stopped.

1. Lee M, Sharifi R. Oxybutynin-induced reflux esophagitis. *DICP Ann Pharmacother* 1990; 24: 583–5.

Effects on the nervous system. A review of adverse CNS effects associated with oxybutynin found 37 reports in children and 143 in adults. Hallucinations were the most common event reported in children, followed by agitation, sedation, confusion, amnesia, and nightmares. Children reported agitation more than twice as often as adults, whereas adults reported sedation more than twice as often as children. Confusion was the most common event reported for patients aged 60 years or over, reported three times as often as for younger patients.[1] A study[2] of healthy subjects, aged 65 years or older, also found oxybutynin to cause cognitive impairment.

1. Gish P, *et al.* Spectrum of central anticholinergic adverse effects associated with oxybutynin: comparison of pediatric and adult cases. *J Pediatr* 2009; 155: 432–4.
2. Katz IR, *et al.* Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc* 1998; 46: 8–13.

Night terrors. Night terrors have been reported in 5 patients taking oxybutynin.[1] Four of the patients were young children and the fifth was an elderly woman. Rechallenge was positive in 2 cases.

1. Valsecia ME, *et al.* New adverse effect of oxybutynin: "night terror". *Ann Pharmacother* 1998; 32: 506.

Overdosage. A report[1] of a 34-year-old woman who ingested 100 mg of oxybutynin. The main symptoms were antimuscarinic effects and included drowsiness, hallucinations, dilatation of pupils, and urinary retention. Tachycardia resolved shortly after admission to hospital but ventricular ectopic beats and bigeminy persisted for over 24 hours. The patient recovered with symptomatic treatment.

1. Banerjee S, *et al.* Poisoning with oxybutynin. *Hum Exp Toxicol* 1991; 10: 225–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxybutynin 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

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Itraconazole. Use of itraconazole with oxybutynin resulted in moderate increases of serum concentrations of the latter.[1] However, concentrations of the active metabolite of oxybutynin, *N*-desethyloxybutynin, were virtually unchanged and the interaction was considered to be of minor clinical significance.

1. Lukkari E, *et al.* Itraconazole moderately increases serum concentrations of oxybutynin but does not affect those of the active metabolite. *Eur J Clin Pharmacol* 1997; 52: 403–6.

Pharmacokinetics

After oral doses of oxybutynin, peak plasma concentrations are reached within one hour. Oxybutynin is also absorbed after application to the skin. It is highly bound to plasma proteins. Oxybutynin undergoes extensive first-pass metabolism, particularly by the cytochrome P450 isoenzyme CYP3A4, and systemic oral bioavailability has been reported to be only 6%. *N*-desethyloxybutynin is an active metabolite. Oxybutynin and its metabolites are excreted in the urine and faeces, and an elimination half-life of 2 to 3 hours has been reported. Oxybutynin has been detected in breast milk. Evidence suggests that it may cross the blood-brain barrier.

References.
1. Gupta SK, Sathyan G. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. *J Clin Pharmacol* 1999; 39: 289–96.
2. Appell RA, *et al.* Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects. *Mayo Clin Proc* 2003; 78: 696–702.
3. Reiz JL, *et al.* Pharmacokinetics and pharmacodynamics of once-daily controlled-release oxybutynin and immediate-release oxybutynin. *J Clin Pharmacol* 2007; 47: 351–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Delak; Ditropan; Oxi-Q; Oxitina; Oxyurin; Retebem; Retemicon; Soxsup†; Tinaxina; Urequin; ***Austral.***: Ditropan; Oxytrol; ***Austria***: Detrusan; Ditropan; Kentera; ***Belg.***: Ditropan; Kentera; ***Braz.***: Frenurin; Incontinol; Retemic; ***Canad.***: Ditropan; Gelnique; Nu-Oxybutyn; Oxytrol; Uromax; ***Chile***: Odranal; Urazol; Uricont; ***China***: Anrushan (安加山)†; Ao Ning (奥宁); Jie Sai (捷赛); Shuang Miao (爽妙); Yi Jing (依静); ***Cz.***: Ditropan; Kentera; Uroxal; ***Denm.***: Kentera; ***Fin.***: Cystrin; Kentera; ***Fr.***: Ditropan; Driptane; ***Ger.***: Dridase; Kentera; Lyrinel†; Oxybugamma; Oxybutin; Oxymedin†; Ryol†; Spasyt†; ***Gr.***: Ditropan; Kentera; Lyrinel; Oxybase; ***Hung.***: Ditropan; Uroxal; ***India***: Cystran; Nocturin; Oxybutin; Oxyspas; ***Irl.***: Cystrin; Ditropan; Kentera; Lyrinel XL; ***Israel***: Lyrinel; Novitropan; ***Ital.***: Ditropan; ***Jpn***: Neoxy; ***Malaysia***: Voxytane; ***Mex.***: Inprax; Lyrinel; Nefryl; Tavor; ***Neth.***: Dridase; Kentera; ***Norw.***: Kentera; ***NZ***: Oxytrol; ***Philipp.***: Driptane; ***Pol.***: Cystrin†; Ditropan; Driptane; Kentera; Uroton; ***Port.***: Ditropan; Kentera; Lyrinel; ***Rus.***: Driptane (Дриптан); Novitropan (Новитропан); ***S.Afr.***: Ditropan; Lenditro; Lyrinel; Oxyspas; Uribexal; ***Singapore***: Lyrinel; Obutin; ***Spain***: Ditropan; Dresplan; ***Swed.***: Ditropan; Kentera; ***Switz.***: Ditropan; Kentera; Lyrinel; ***Thai.***: Diutropan; Lyrinel; ***Turk.***: Uropan; ***UK***: Cystrin; Ditropan; Kentera; Lyrinel XL; ***Ukr.***: Driptane (Дриптан); Sibutin (Сибутин); ***USA***: Anturol†; Ditropan; Gelnique; Oxytrol; ***Venez.***: Reteven.

Pharmacopoeial Preparations

BP 2014: Oxybutynin Oral Solution; Oxybutynin Tablets; Prolonged-release Oxybutynin Tablets;
USP 36: Oxybutynin Chloride Extended-Release Tablets; Oxybutynin Chloride Syrup; Oxybutynin Chloride Tablets.

Papaverine *(BAN)*

Papaverilini; Papaverin; Papaverina; Papaverinum; Папаверин.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline.

$C_{20}H_{21}NO_4$=339.4

CAS — 58-74-2.

ATC — A03AD01; G04BE02.

ATC Vet — QA03AD01; QG04BE02.

UNII — DAA13NKG2Q.

NOTE. Papaverine should not be confused with papaveretum (p. 112.2).

Papaverine Hydrochloride *(BANM)*

Papaverilinihydrokloridi; Papaverina, hidrocloruro de; Papavérine, chlorhydrate de; Papaverin-hidroklorid; Papaverinhydrochlorid; Papaverinhydrochlorid; Papaverinhydrokloridi; Papaverini hydrochloridum; Papaverinii Chloridum; Papaverinium Chloride; Papaverino hidrochloridas; Papaweryny chlorowodorek; Папаверина Гидрохлорид.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline hydrochloride.

$C_{20}H_{21}NO_4$.HCl=375.8

CAS — 63817-84-5 (papaverine cromesilate); 61-25-6 (papaverine hydrochloride); 39024-96-9 (papaverine monophosadenine); 2053-26-1 (anhydrous papaverine sulfate).

ATC — A03AD01; G04BE02.

ATC Vet — QA03AD01; QG04BE02.

UNII — 23473EC6BQ.

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

Ph. Eur. 8: (Papaverine Hydrochloride). White or almost white crystals or crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 3.0 to 4.0.

USP 36: (Papaverine Hydrochloride). Odourless white crystals or white, crystalline powder. Soluble 1 in 30 of water and 1 in 120 of alcohol; soluble in chloroform; practically insoluble in ether. pH of a 2% solution in water is between 3.0 and 4.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Papaverine is an alkaloid present in opium, although it is not related chemically or pharmacologically to the other opium alkaloids. Papaverine has a direct relaxant effect on smooth muscle which is attributed in part to its ability to inhibit phosphodiesterase. It has been given in the management of cerebral, peripheral, and coronary **vascular disorders**; it is also given as an **antispasmodic** for gastrointestinal disorders and coughs. However, there is little evidence to justify its clinical use in these conditions.

Papaverine hydrochloride has been given orally in doses of up to 600 mg daily. Sustained-release preparations have been used. The codecarboxylase derivative, cromesilate, hydrobromide, monophosadenine, nicotinate, sulfate, and teprosilate have also been used. Papaverine hydrochloride has also been given in doses of 30 to 120 mg by intramuscular or slow intravenous injection, repeated every 3 hours as needed (but see Adverse Effects and Precautions, below).

Papaverine hydrochloride has been given by injection into the corpus cavernosum of the penis for the treatment of **erectile dysfunction** (p. 2348.2). Doses have ranged from 2.5 to 60 mg, but must be initially titrated by the prescriber. Doses up to about 30 mg have been combined with phentolamine.

Adverse Effects and Precautions

Adverse effects of oral papaverine include gastrointestinal disturbance, flushing of the face, headache, malaise, drowsiness, skin rash, sweating, orthostatic hypotension, and dizziness. Jaundice, eosinophilia, and signs of altered liver function may occur, sometimes due to hypersensitivity. In addition high parenteral doses can result in cardiac arrhythmias; intravenous or intramuscular doses should be given slowly. Thrombosis has been reported at the injection site.

Intracavernosal injection can cause dose-related priapism and local fibrosis has been reported after long-term therapy.

Papaverine should be given with caution to patients with reduced gastrointestinal motility. Caution is also advised in the presence of cardiac conduction disorders or unstable cardiovascular disease, especially when papaverine is given parenterally. Intravenous dosage is contra-indicated in patients with complete AV block.

Glaucoma. There appeared to be no basis for the manufacturers' recommendation that papaverine should be used with caution in patients with glaucoma.[1] There was no obvious mechanism to support such a warning and only 1 report of an adverse reaction had been received by the FDA. The author had given papaverine intracavernosally to patients with glaucoma and had seen no deterioration.

1. Swartz DA, Todd MW. Intracavernous papaverine and glaucoma. *JAMA* 1990; 264: 570.

Intracavernosal administration. Systemic adverse effects occurring after intracavernosal injection of papaverine are infrequent but include dizziness and syncope,[1,2] probably

related to the hypotensive effects of papaverine; abnormal liver function test results have also occurred.[1-3]

The most serious acute adverse effect is priapism[1,2,4] and patients should be instructed to seek medical help if an erection lasts for more than 4 hours. Detumescence can be effected by aspiration of blood from the corpus or by local injection of an alpha-adrenergic agonist such as adrenaline, metaraminol, or phenylephrine (see Priapism under Alprostadil, p. 2353.2). Other local effects include haematoma, infection, and, on long-term therapy, fibrosis and penile distortion.[1,2]

Dispensing errors have resulted in inadvertent injection of *papaveretum* with potentially fatal consequences.[2,5,6]

1. Krane RJ, *et al.* Impotence. *N Engl J Med* 1989; 321: 1648–59.
2. Bénard F, Lue TF. Self-administration in the pharmacological treatment of impotence. *Drugs* 1990; 39: 394–8.
3. Levine SB, *et al.* Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence. *J Urol (Baltimore)* 1989; 141: 54–7.
4. Virag R. About pharmacologically induced prolonged erection. *Lancet* 1985; i: 519–20.
5. Robinson LQ, Stephenson TP. Self injection treatment for impotence. *BMJ* 1989; 299: 1568.
6. Gregoire A. Self injection treatment for impotence. *BMJ* 1990; 300: 537.

Interactions

Levodopa. For the effects of papaverine on levodopa, see p. 908.1.

Pharmacokinetics

The biological half-life of papaverine given orally is reported to be between 1 and 2 hours, but there is wide interindividual variation. It is about 90% bound to plasma proteins.

Papaverine is mainly metabolised in the liver and excreted in the urine, almost entirely as glucuronide-conjugated phenolic metabolites.

The reports of infrequent systemic effects after intracavernosal injection of papaverine indicate that there is some distribution to the systemic circulation from the corpus cavernosus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mesotina; *China*: Bo Wei (泊威); Fei Lin (菲林); FuHong (福虹); Gai Yi (盖一); Kai Ge La Fei (凯格拉非); Kuo Shu (阔舒); Sai De Long (赛德隆); *India*: Paparin; *Venez.*: Atroveran; Papaveryl.

Multi-ingredient Preparations. *Arg.*: Antipasmol; Antispasmina; Gastranil; Hepatodirectol; Neoastrin; *Austria*: Androskat; *Braz.*: Ductoveran; Espasmocron†; Monotrean B6; Monotrean; Sedalene; Sedalin†; Spasmotropin; Vagostesyl; *Chile*: Buton; Colicor; Dipatropin; Dolospam; *Fr.*: Acticarbine; *Hong Kong*: Codolax†; Codoplex; Codoplex; Enterocin Compound†; Methor-Co†; Metoplex; Vickolax†; *Hung.*: Meristin; Neo-Bilagit; Troparinum; *India*: Brovon; *Indon.*: Sanmag; Spaslic; Spasmal; Spasminal†; *Israel*: Spasmalgin; *Ital.*: Antispasmina Colica; *Mex.*: Acilin; *Neth.*: Androskat; *Pol.*: Biospasmil†; Fortestomachicae; Spasticol; Tolargin†; *Port.*: Antispasmina Colica†; *Rus.*: Andipal (Андипал); Pagluferal (Паглюферал); Papazol (Папазол); *Spain*: Sulmetin Papaver†; *Swed.*: Spasmofen; *Switz.*: Spasmosol†; *UK*: Brovon; *USA*: Tri-Mix; *Venez.*: Atrobel.

Pharmacopoeial Preparations
BP 2014: Papaverine Injection;
USP 36: Papaverine Hydrochloride Injection; Papaverine Hydrochloride Tablets.

Propiverine Hydrochloride

(BANM, rINNM)

BUP-4 (propiverine); Hidrocloruro de propiverina; Propiverin Hidroklorür; Propiverina, hidrocloruro de; Propivérine, Chlorhydrate de; Propiverini Hydrochloridum; Пропиверина Гидрохлорид.

1-Methyl-4-piperidyl diphenylpropoxyacetate hydrochloride.

$C_{23}H_{29}NO_3$,HCl=403.9

CAS — 60569-19-9 (propiverine); 54556-98-8 (propiverine hydrochloride).

ATC — G04BD06.

ATC Vet — QG04BD06.

Uses and Administration

Propiverine hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used for the management of urinary frequency, urgency, and incontinence (p. 2349.2) in neurogenic bladder disorders and in idiopathic detrusor instability. Usual oral doses of propiverine hydrochloride are 15 mg two or three times daily, increased to 4 times daily if required. Some patients may respond to 15 mg once daily. A daily dose of 60 mg should not be exceeded. Propiverine hydrochloride can also be given as a modified-release preparation in a dose of 30 mg once daily.

Administration in hepatic impairment. Although UK licensed product information for propiverine does not recommend its use in patients with moderate or severe hepatic impairment some[1] suggest that on pharmacokinetic grounds it may be given to those with mild to moderate degrees of impairment at recommended doses without increasing the risk of adverse effects.

1. Siepmann M, *et al.* Pharmacokinetics and safety of propiverine in patients with fatty liver disease. *Eur J Clin Pharmacol* 1998; 54: 767–71.

Urinary incontinence. Although propiverine is licensed in the UK for use in urinary frequency, urgency, and incontinence (see above), guidelines subsequently issued by NICE consider that although it should be an option for urinary frequency in women with overactive bladder syndrome, use in women with overt incontinence is not recommended.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1. Hypotension and drowsiness may also occur with propiverine. Propiverine is contra-indicated in patients with moderate or severe hepatic impairment (but see above). Liver enzyme values should be monitored in patients receiving long-term therapy. Skeletal retardation has occurred in the offspring of *animals* given high doses of propiverine during pregnancy and therefore its use is not recommended during pregnancy.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Hypotension may occur in patients treated with propiverine and isoniazid. Drowsiness may be enhanced by drugs with CNS-depressant properties.

Pharmacokinetics

Propiverine is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2.3 hours after oral doses. It undergoes extensive first-pass metabolism and the average absolute bioavailability is reported to be about 41%. Plasma concentrations of the principal metabolite, the *N*-oxide, greatly exceed those of the parent compound. Protein binding is about 90% for propiverine and 60% for the *N*-oxide metabolite. Propiverine and its metabolites are excreted in the urine, bile, and faeces. The elimination half-life is about 20 hours.

References.
1. Haustein K-O, Hüller G. On the pharmacokinetics and metabolism of propiverine in man. *Eur J Drug Metab Pharmacokinet* 1988; 13: 81–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Mictonorm; *China*: He Er Shu (贺尔舒); Hua Ke (华克); PeiNing (培宁); *Cz.*: Mictonetten; Mictonorm; *Ger.*: Mictonetten; Mictonorm; Propimedac; Propiver; *Gr.*: Mictonorm; *Hong Kong*: Mictonorm; *Indon.*: Mictonorm; *Irl.*: Detrunorm; Propinorm; *Jpn*: BUP-4; *Philipp.*: Mictonorm; *Port.*: Mictonorm; *S.Afr.*: Detrunorm; *Singapore*: Mictonorm; *Thai.*: Mictonorm†; *Turk.*: Mictonorm; *UK*: Detrunorm.

Pygeum Africanum

African Prune; Afrikankirsikkapuunkuori (pygeum africanum bark); Afrikinių slyvų žievė (pygeum africanum bark); Kůra slivoně africké (pygeum africanum bark); Pigeum; Pruni Africanae; Pruni africanae cortex (pygeum africanum bark); Prunier d'Afrique; Prunier d'Afrique, écorce de (pygeum africanum bark); Африканская Слива.

ATC — G04CX01.

ATC Vet — QG04CX01.

ATC Herb — HG04CW5007 (Prunus africana: bark).

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

Ph. Eur. 8: (Pygeum Africanum Bark; Pygeum Bark BP 2014). The whole or cut, dried bark of the stems and branches of *Prunus africana* (*Pygeum africanum*).

USP 36: (Pygeum). The bark of *Prunus africana* (*Pygeum africanum*) (Rosaceae). It contains not less than 9.0% of extractable matter.

Profile

An extract from the bark of the tree *Prunus africana* (*Pygeum africanum*) is used in the treatment of benign prostatic hyperplasia (p. 2347.1). Like some other phytotherapies for this disorder, it appears to contain various sitosterols. A usual oral dosage is 100 mg daily.

Benign prostatic hyperplasia. Pygeum africanum appears to produce a modest benefit on urological symptoms and measures of urinary flow.

References.
1. Andro M-C, Riffaud J-P. Pygeum africanum extract for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience. *Curr Ther Res* 1995; 56: 796–817.
2. Buck AC. Phytotherapy for the prostate. *Br J Urol* 1996; 78: 325–36.
3. Ishani A, *et al.* Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med* 2000; 109: 654–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Prostem; *China*: Tadenan (太得恩); *Cz.*: Tadenan†; *Fr.*: Tadenan; *Gr.*: Foudaril; Rotamat; Tadenan; *Ital.*: Pigenil; *Mex.*: Tadenom; *Philipp.*: Tadenan; *Pol.*: Poldanen; Tadenan; *Rus.*: Tadenan (Таденан); Trianol (Трианол); *Spain*: Acubiron†; Bidrolar†; Pronitol†; Tuzanil; *Switz.*: Tadenan; *Thai.*: Tadenan; *Ukr.*: Tadenan (Таденан); Trianol (Трианол)†.

Multi-ingredient Preparations. *Arg.*: Catiz Plus; Normoprost Compuesto; Normoprost Plus; Ultracal; *Belg.*: Prostatonin†; *Braz.*: Prostem Plus; *Canad.*: Prosta Ease; Prostease; *Fr.*: Prosta-SecurA; *Hong Kong*: Prostease; *Hung.*: Prostatonin; *Pol.*: Neo-poldanen†; *Port.*: Neo Urgenin; *Spain*: Neo Urgenin†; Prosturol; Tebetane Compuesto; *Switz.*: Prostatonin; *UK*: Potenzia.

Pharmacopoeial Preparations
USP 36: Pygeum Capsules.

Saw Palmetto

American Dwarf Palm; *Brahea serrulata*; *Sabal serrulata*; *Serenoa repens*; *Serenoa serrulatum*; PA-109; Palma enana americana; Palmera de Florida; Sabal; Sabal, fruit de (saw palmetto fruit); Sabalis Serrulatae; Sabalis serrulatae fructus (saw palmetto fruit); Sågpalmettofrukt (saw palmetto fruit); Sahapalmunhedelmä (saw palmetto fruit); Serenový plod (saw palmetto fruit); Šliaužiančiųjų serenojų vaisiai (saw palmetto fruit); Пальма Серенoа.

ATC — G04CX02.

ATC Vet — QG04CX02.

ATC Herb — HG04CW5008 (Serenoa repens: fruit).

UNII — 487DXM62F2 (Serenoa repens); J7WWH9M8QS (Serenoa repens fruit).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*. *Eur.* and *US* also include the extract. *US* also includes the powdered form.

Ph. Eur. 8: (Saw Palmetto Fruit). The dried, ripe fruit of *Serenoa repens* (*Sabal serrulata*). It has a strong, but not rancid, odour. It contains not less than 11.0% of total fatty acids, calculated with reference to the dried drug.

USP 36: (Saw Palmetto). The partially dried, ripe fruit of *Serenoa repens* (Arecaceae). Store in airtight containers. Protect from light.

Profile

The dried fruit of the saw palmetto or American dwarf palm tree, *Serenoa repens* (Arecaceae), contains steroidal compounds with anti-androgenic and oestrogenic activities, one of which is sitosterol (p. 1471.2). Saw palmetto is used for the treatment of benign prostatic hyperplasia. Preparations of alcoholic or lipophilic extracts of the fruit have typically been given in oral doses of 160 mg twice daily, or 320 mg once daily.

Adverse effects. A systematic review of the adverse effects of saw palmetto, including data from international and national reporting schemes, clinical studies, case reports, and manufacturers, found the most frequent adverse effects to be gastrointestinal disturbances, abdominal pain, fatigue, headache, decreased libido, and rhinitis. There was one report of hypokalaemia leading to fatality received by the Australian national reporting scheme (ADRAC).[1]

1. Agbabiaka TB, *et al.* Serenoa repens (saw palmetto): a systematic review of adverse events. *Drug Safety* 2009; 32: 637–47.

EFFECTS ON THE LIVER. Cholestatic hepatitis occurred in a man who took a herbal preparation containing saw palmetto for 2 weeks to treat nocturia and hesitancy.[1]

1. Hamid S, *et al.* Protracted cholestatic hepatitis after the use of Prostata. *Ann Intern Med* 1997; 127: 169–70.

Uses. *BENIGN PROSTATIC HYPERPLASIA.* A lipid hexane extract of saw palmetto has been shown to be generally superior to placebo,[1,2] and of similar efficacy to finasteride[3] in the treatment of benign prostatic hyperplasia (p. 2347.1). However, a double-blind study[4] found that treatment for one year was not superior to placebo for improving

urinary symptoms and objective measures. A subsequent systematic review of 30 randomised studies of various saw palmetto extracts concluded that they did not improve urological symptoms and flow measures in men with benign prostatic hyperplasia.[5]

1. Champault G, *et al.* A double-blind trial of an extract of the plant Serenoa repens in benign prostatic hyperplasia. *Br J Clin Pharmacol* 1984; 18: 461.
2. Plosker GL, Brogden RN. Serenoa repens (Permixon): a review of its pharmacology and therapeutic efficacy in benign prostatic hyperplasia. *Drugs Aging* 1996; 9: 379–95.
3. Carraro J-C, *et al.* Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate* 1996; 29: 231–40.
4. Bent S, *et al.* Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 2006; 354: 557–66.
5. Tacklind J, *et al.* Serenoa repens for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 15/01/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Beltrax Uno; Permicaps; Permixon; Serecur; *Austral.*: Pro-Guard†; Prostate Defence; *Austria*: Permixon; Prosta-Urgenin; Prostasan; Sabal; *Belg.*: Prosta-Urgenin: Prostaserene; *Braz.*: Prostat; Prostatal; Renopen; *Canad.*: Sabalasan; *Chile*: Prostafort; Sabal; *China*: Prostadyn (前诺特); *Cz.*: Capistan; Prosta-Urgenin; Prostakan Mono; Prostamol Uno; Spalda Sabal; *Fin.*: Curbisal; Prostacaps†; Prostaforce; *Fr.*: Permixon; Prodinan; Sabal; *Ger.*: Cefasabal†; Eviprostat-S; Horphagen uno; Hyperprost; Prosta Urgenin Uno; Prostagutt mono; Prostagutt uno; Prostess; Remiprostan uno; Sabal uno; Sabal; Sabalvit; Sita†; Steiprostat; Strogen; Talsot†; *Gr.*: Libeprosta; Urisedon; *Hong Kong*: Permixon; *Hung.*: Prostamol Uno; Saballo; Strogen Uno; *Indon.*: Lanaprost†; Prostakurt†; *Israel*: Permixon; *Ital.*: Permixon: Prosteren: Riiaprost; Saba; Serpens: *Malaysia*: Lanaprost; *Mex.*: Permixon: Prostasan; Prostex; Urogutt; *Norw.*: Curbisal; Fitoprost; *Philipp.*: Prostacare; ProstActive; *Pol.*: Bioprost; Fitoprost: Permixon†; Prostaforce; Prostamol Uno; Prostaplant; Sterko; *Port.*: Permixon; Sereprosta; *Rus.*: Permixon (Пермиксон); Prostamol Uno (Простамол Уно); Prostaplant (Простаплант); *Singapore*: Lanaprost; Permixon; Prostakan; *Spain*: Permixon; Sereprostat; *Swed.*: Curbisal; Sabamin; *Switz.*: Permixon; Prosta-Urgenine; Prostadyn; Prostagutt uno; ProstaMed; Prostasan; SabCaps; *Thai.*: Blackmores Prosereu; Permixon; Prosta-Urgenin; Sametto; Urogutt; *Turk.*: Prostagood; *UK*: Prostasan; Sabal; Sabalin; *Ukr.*: Prosta Urgenin Uno (Проста Ургенин Уно)†; Prostacer (Простакер); Prostamol Uno (Простамол Уно); Prostaplant (Простаплант); *Venez.*: Chronostim.

Multi-ingredient Preparations. *Arg.*: ADX; Anastim; Argeal; Catiz Plus; Keracnyl; Keracnyl; Normoprost Plus; Novo Prostasan; PR21; Sabal; Troxac; Ultracal; *Austral.*: Advanced Prostate Care; Extralife Flow-Care†; Masculine Herbal Complex; Mens Dual-Action Multi; Mens Super Soy/Clover†; Prosta Balance; ProstaCo; Prostate Health Formula; *Austria*: Prostagutt; Spasmo-Urgenin; Urgenin; Urogutt; *Belg.*: Prostalane†; Urgenin; *Braz.*: Capilos; *Canad.*: Prosta Ease; Prostease; Saw Palmetto Formula†; *Chile*: Argeal; Keracnyl; *Cz.*: Prostakan Forte; *Fr.*: Argeal; Kelual DS; Keracnyl; Keracnyl; Kertyol Sbampooing†; ProstaSecurA; *Ger.*: Cefasabal†; Granu Fink Prosta; Nephroselect M; Prostagutt forte; *Hong Kong*: Palmetto Plus†; PhytoEase; Prostease; Urgenin†; *Hung.*: Prostazyn; *Indon.*: Instink†; Maxirex; Menolia†; Reximax; Soprost†; *Israel*: Urgenin†; *Ital.*: Bioesse Plus; Biothymus M; Pluvio; Prostaplant; Sametrix; *Malaysia*: Cefasabal; *Mex.*: Prosgutt; *Pol.*: Naturapia Prostata†; Penigra; *Port.*: Efluvium Anti-caspa†; Efluvium Anti-seborreico†; Neo Urgenin; *Rus.*: Prostagutt Forte (Простагут Форте); *Singapore*: Palmetto Plus†; *Spain*: Neo Urgenin†; Spasmo-Urgenin; Urgenin†; *Switz.*: Granu Fink Prosta†; Prostagutt-F; *Thai.*: Spasmo-Urgenin; *UK*: Antiglan; Daily Fatigue Relief; Damiana and Kola Tablets; Elixir Damiana and Saw Palmetto; Potenzia; Regina Royal Concorde; Strength; *Ukr.*: Prostaplant Forte (Простаплант Форте); *USA*: Alive Mens Energy; Clinical Nutrients 50-Plus Men; Udamin SP; *Venez.*: Argeal; Sabal.

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; Cantharis Med Complex; Erbiode-Starkungstropfen; Gentos; Prosfortil; *Canad.*: Breast Enhancer; Male +; Reneel†; *Fr.*: Juniperus Complexe No 6; Sabal Serrulata Compose; *Ger.*: Cysto Hevert; Hewesabal mono†; Homvio-Rin; Pascosabal; Prostamed Mikto; Prostasabal; Prostata-Entoxin N; Prostata-Gastreu N R25; Prostata-Komplex L Ho-Fu-Complex; Prostata-Komplex N Ho-Fu-Complex†; Urofossat; Urokatt; Urotruw N; Ursinol; *Hung.*: Gentos; *Neth.*: Reneel H; Sabal-Homaccord; *Rus.*: Gentos (Гентос); Sabal-Homaccord (Сабаль-Гомаккорд); *Switz.*: Regenaplex Nr. 49a; *Ukr.*: Gentos (Гентос); Homvio-Prostan (Хомвио-Простан).

Pharmacopoeial Preparations

USP 36: Saw Palmetto Capsules.

Sildenafil Citrate *(BANM, USAN, rINNM)*

Citrato de sildenafilo; Sildénafil, citrate de; Sildenafil Sitrat; Sildenafill citras; Sildenafilo, citrato de; UK-92480-10; Сильденафила Цитрат.

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1,6-dihydro-1-methyl-3-propylpyrazolo[4,3-*d*]pyrimidin-7-one citrate; 1-{[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazone citrate.

$C_{22}H_{30}N_6O_4S,C_6H_8O_7$=666.7

CAS — 139755-83-2 (sildenafil); 171599-83-0 (sildenafil citrate).

ATC — G04BE03.

ATC Vet — QG04BE03.

UNII — BW9B0ZE037.

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

Ph. Eur. 8: (Sildenafil Citrate). A white or almost white, slightly hygroscopic, crystalline powder. Slightly soluble in water and in methyl alcohol; practically insoluble in hexane. Store in airtight containers.

USP 36: (Sildenafil Citrate). A white or almost white, slightly hygroscopic, crystalline powder. Slightly soluble in water and in methyl alcohol; practically insoluble in hexane. Store in airtight containers.

Stability. Sildenafil citrate tablets were ground to a powder and combined with a 1:1 mixture of methylcellulose 1% and simple syrup (USNF), or with a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (both *Paddock, USA*), to a nominal concentration of 2.5 mg/mL sildenafil citrate in each suspension.[1] Both suspensions were found to be chemically and physically stable for 91 days in plastic bottles, at both 4 degrees and 25 degrees.

1. Nahata MC, *et al.* Extemporaneous sildenafil citrate oral suspensions for the treatment of pulmonary hypertension in children. *Am J Health-Syst Pharm* 2006; 63: 254–7.

Uses and Administration

Sildenafil is a phosphodiesterase type-5 inhibitor used in the management of erectile dysfunction and pulmonary arterial hypertension (see below and p. 2365.1 respectively for more details). It can be given orally, or by intravenous injection, as the citrate although doses are expressed in terms of the base; 14 mg of sildenafil citrate is equivalent to about 10 mg of sildenafil.

In **erectile dysfunction**, it is given orally, in a usual dose equivalent to sildenafil 50 mg about one hour before sexual intercourse. The dose may be increased or decreased depending on response. The maximum recommended dose is 100 mg, and sildenafil should not be taken more than once in 24 hours.

- An initial dose of 25 mg has been suggested in the USA for patients over 65 years of age, though such initial reductions are not considered necessary in the UK.
- An initial dose of no more than 25 mg daily is advised in patients taking sildenafil with inhibitors of cytochrome P450 isoenzyme CYP3A4; the dose should not exceed 25 mg every 48 hours if given with ritonavir-boosted HIV-protease inhibitors, although such a combination is best avoided entirely (see Interactions, p. 2366.3).
- In patients stabilised on alpha blocker therapy, an initial dose of sildenafil 25 mg should be considered.

To improve exercise ability in **pulmonary arterial hypertension**, sildenafil is given orally in a dose of 20 mg three times daily. Alternatively, it may be given by intravenous injection in a dose of 10 mg three times daily if the oral route is not possible. Use of sildenafil for pulmonary arterial hypertension is not recommended with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir; use with other potencies of CYP3A4 inhibitor may require a reduction in the sildenafil dose. In the UK, a dose reduction to 20 mg twice daily orally, or 10 mg twice daily intravenously, should be considered in patients taking sildenafil with medium-potency CYP3A4 inhibitors like erythromycin or unboosted saquinavir. A reduction to 20 mg once daily orally, or 10 mg once daily intravenously, is advised in patients taking sildenafil with stronger CYP3A4 inhibitors like clarithromycin, telithromycin, and nefazodone.

For doses in children, see Administration in Children below.

For doses in hepatic and renal impairment, see below.

Administration in children. Sildenafil citrate may be given *orally* to children for the treatment of pulmonary arterial hypertension. In Europe it is licensed for use in those aged from 1 to 17 years. The dose for those weighing 20 kg or less is 10 mg three times daily, and for those weighing over 20 kg [about 6 years or older] it is 20 mg three times daily (the same as the licensed adult dose). The *BNFC* suggests that neonates and children up to 1 year may be given an initial dose of 250 to 500 micrograms/kg every 4 to 8 hours, adjusted according to response to a maximum of 30 mg daily. Tapered withdrawal is advised.

Although unlicensed in neonates and children, *intravenous* sildenafil has been used successfully. In a dose-finding study involving 36 neonates with persistent pulmonary hypertension,[1] an intravenous loading dose of 400 micrograms/kg given over 3 hours, followed by a maintenance infusion (for 48 hours to 7 days) of 1.6 mg/kg daily improved oxygenation scores and was well tolerated.

1. Steinhorn RH, *et al.* Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. *J Pediatr* 2009; 155: 841–7.

Administration in hepatic impairment. Sildenafil clearance is reduced in patients with hepatic impairment. Safety has not been established in patients with severe hepatic impairment (Child-Pugh class C) and its use is contra-indicated in these patients for this reason.

Licensed product information for patients with **erectile dysfunction** recommends an initial oral dose of 25 mg in patients with hepatic impairment.

Licensed product information for patients with **pulmonary arterial hypertension** states that initial dose adjustments are not needed for patients with mild or moderate hepatic impairment (Child-Pugh class A or B); in the UK, it is recommended that a reduction to 20 mg twice daily orally, or 10 mg twice daily intravenously, should be considered if therapy is not well tolerated.

Administration in renal impairment. Sildenafil clearance is reduced in patients with severe renal impairment.

Licensed product information for patients with **erectile dysfunction** recommends that in these patients, an initial oral dose of 25 mg should be considered. In the UK it is stated that the dose may be increased to 50 or 100 mg orally, if needed and tolerated.

Licensed product information for patients with **pulmonary arterial hypertension** states that no dose adjustments are required for patients with renal impairment, including those with severe renal impairment (creatinine clearance less than 30 mL/minute). However, in the UK, consideration of a reduction to 20 mg twice daily orally, or 10 mg twice daily intravenously, is suggested if therapy is not well tolerated.

Benign prostatic hyperplasia. Although not routinely recommended due to a lack of data, sildenafil has been used to treat lower urinary tract symptoms commonly associated with benign prostatic hyperplasia (p. 2347.1).[1]

1. Gales BJ, Gales MA. Phosphodiesterase-5 inhibitors for lower urinary tract symptoms in men. *Ann Pharmacother* 2008; 42: 111–15.

Erectile dysfunction. Sildenafil, an inhibitor of phosphodiesterase type-5, is used as an oral therapy for erectile dysfunction (p. 2348.2). It is effective in erectile dysfunction of psychogenic causes and organic causes such as diabetes mellitus, spinal-cord injury, and prostatectomy.

References.

1. Langtry HD, Markham A. Sildenafil: a review of its use in erectile dysfunction. *Drugs* 1999; 57: 967–89.
2. Montorsi F, *et al.* Efficacy and safety of fixed-dose oral sildenafil in the treatment of erectile dysfunction of various etiologies. *Urology* 1999; 53: 1011–18.
3. Rendell MS, *et al.* Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. *JAMA* 1999; 281: 421–6.
4. Kedia S, *et al.* Treatment of erectile dysfunction with sildenafil citrate (Viagra) after radiation therapy for prostate cancer. *Urology* 1999; 54: 308–12.
5. Zippe CD, *et al.* Role of Viagra after radical prostatectomy. *Urology* 2000; 55: 241–5.
6. Fink HA, *et al.* Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2002; 162: 1349–60.
7. Fedele D, *et al.* Experience with sildenafil in diabetes. *Diabetes Nutr Metab* 2002; 15: 49–52.
8. Derry F, *et al.* Efficacy and safety of sildenafil citrate (Viagra) in men with erectile dysfunction and spinal cord injury: a review. *Urology* 2002; 60 (suppl): 49–57.
9. Raina R, *et al.* Long-term effect of sildenafil citrate on erectile dysfunction after radical prostatectomy: 3-year follow-up. *Urology* 2003; 62: 110–15.
10. Carson CC. Sildenafil: a 4-year update in the treatment of 20 million erectile dysfunction patients. *Curr Urol Rep* 2003; 4: 488–96.
11. Setter SM, *et al.* Phosphodiesterase 5 inhibitors for erectile dysfunction. *Ann Pharmacother* 2005; 39: 1286–95.

Female sexual dysfunction. Improvements have been reported in women with antidepressant-associated sexual dysfunction after treatment with sildenafil compared with placebo.[1] A review[2] concluded that, although data suggest a possible role for sildenafil for the treatment of female sexual dysfunction, studies are small and of variable quality, and should be interpreted with caution.

1. Nurnberg HG, *et al.* Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *JAMA* 2008; 300: 395–404.
2. Brown DA, *et al.* Assessing the clinical efficacy of sildenafil for the treatment of female sexual dysfunction. *Ann Pharmacother* 2009; 43: 1275–85.

High-altitude disorders. Hypoxic pulmonary hypertension associated with high altitude (p. 1276.2) may respond to sildenafil. Small studies have shown some promising results.[1-3]

1. Ghofrani HA, *et al.* Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp: a randomized, double-blind, placebo-controlled crossover trial. *Ann Intern Med* 2004; 141: 169–77.
2. Richalet JP, *et al.* Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. *Am J Respir Crit Care Med* 2005; 171: 275–81.
3. Ricart A, *et al.* Effects of sildenafil on the human response to acute hypoxia and exercise. *High Alt Med Biol* 2005; 6: 43–9.

Oesophageal motility disorders. Preliminary studies[1-3] have investigated the use of sildenafil in patients with oesophageal motility disorders (p. 1813.2) such as achalasia or nutcracker oesophagus. Although some benefit has been reported, further studies are needed.

1. Bortolotti M, *et al.* Effects of sildenafil on esophageal motility of patients with idiopathic achalasia. *Gastroenterology* 2000; 118: 253–7.
2. Eherer AJ, *et al.* Effect of sildenafil on oesophageal motor function in healthy subjects and patients with oesophageal motor disorders. *Gut* 2002; 50: 758–64.
3. Lee JI, *et al.* The effect of sildenafil on oesophageal motor function in healthy subjects and patients with nutcracker oesophagus. *Neurogastroenterol Motil* 2003; 15: 617–23.

Premature ejaculation. Early reports have suggested that sildenafil may be effective in the management of premature ejaculation (p. 2350.2) and the rationale for such use has been reviewed.[1]

1. Abdel-Hamid IA. Phosphodiesterase 5 inhibitors in rapid ejaculation: potential use and possible mechanisms of action. *Drugs* 2004; 64: 13–26.

Priapism. Sildenafil has been reported to be effective in the treatment of priapism in 3 patients with sickle-cell disease.[1] In 2 of these patients, sildenafil was also successful in preventing further episodes of priapism when it was taken at the onset of symptoms.

1. Bialecki ES. Sildenafil relieves priapism in patients with sickle cell disease. *Am J Med* 2002; 113: 252.

Pulmonary hypertension. Oral phosphodiesterase type-5 inhibitors have produced beneficial responses in patients with pulmonary arterial hypertension (p. 1278.2), and sildenafil and tadalafil may be used as first- or second-line therapy in patients in functional class II or III. The results of short-term and long-term studies of phosphodiesterase type-5 inhibitors have been reviewed.[1-3] In a study[4] using single doses of phosphodiesterase type-5 inhibitors, it was found that sildenafil and tadalafil had greater selectivity for the pulmonary circulation than vardenafil, and that arterial oxygenation was improved by sildenafil only. Sildenafil, with which most experience lies, has been given either alone[5-7] or with other treatments such as inhaled nitric oxide,[6] inhaled iloprost,[8] intravenous epoprostenol,[9-11] oral beraprost,[12] or oral bosentan.[13,14] In a pivotal study,[7] sildenafil improved exercise capacity and haemodynamics in patients when given at 20, 40, or 80 mg orally three times daily. While there was no evidence of a dose-response relationship in the primary end-point of exercise capacity, there was a linear trend in the response in haemodynamic measures. In an extension study, all patients were treated with 80 mg orally three times daily if tolerated. Some have questioned whether the licensed dose of 20 mg three times daily is sufficient,[15] especially if patients are given bosentan at the same time (the two drugs interact—see Cardiovascular Drugs under Interactions, p. 2366.3). This led the authors of the original study to suggest that the licensed dose be used initially, with an increase to 40 or 80 mg three times daily in order to achieve or maintain favourable effects.[16]

Where there is associated cirrhosis (portopulmonary hypertension) it has been suggested that sildenafil may be useful in stabilising symptoms sufficiently to facilitate transplantation.[17]

Sildenafil has also been studied for paediatric pulmonary hypertension, including persistent pulmonary hypertension in neonates and in those with pulmonary arterial hypertension associated with congenital heart disease, or secondary to lung disease, or in postoperative pulmonary hypertension and in neonates who are difficult to wean from inhaled nitric oxide.[18-21] Licensed and unlicensed paediatric doses are given under Administration in Children, p. 2364.2.

Sildenafil has also been reported to be of benefit in high-altitude pulmonary hypertension,[22] and has been tried in pulmonary hypertension associated with chronic thromboembolic disorders.[23]

1. Croom KF, Curran, MP. Sildenafil: a review of its use in pulmonary arterial hypertension. *Drugs* 2008; 68: 383–97.
2. Archer SL, Michelakis ED. Phosphodiesterase type 5 inhibitors for pulmonary arterial hypertension. *N Engl J Med* 2009; 361: 1864–71.
3. Buckley MS, *et al.* Phosphodiesterase-5 inhibitors in management of pulmonary hypertension: safety, tolerability, and efficacy. *Drug Healthc Patient Saf* 2010; 2: 151–61.
4. Ghofrani HA, *et al.* Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. *J Am Coll Cardiol* 2004; 44: 1488–96.
5. Sastry BKS, *et al.* Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. *J Am Coll Cardiol* 2004; 43: 1149–53.
6. Michelakis E, *et al.* Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. *Circulation* 2002; 105: 2398–2403.
7. Galiè N, *et al.* Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; 353: 2148–57.
8. Ghofrani HA, *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; 136: 515–22.
9. Bhatia S, *et al.* Immediate and long-term hemodynamic and clinical effects of sildenafil in patients with pulmonary arterial hypertension receiving vasodilator therapy. *Mayo Clin Proc* 2003; 78: 1207–13.
10. Stiebellehner L, *et al.* Long-term treatment with oral sildenafil in addition to continuous IV epoprostenol in patients with pulmonary arterial hypertension. *Chest* 2003; 123: 1293–5.
11. Simonneau G, *et al.* PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008; 149: 521–30. Correction. *ibid.* 2009; 150: 63.
12. Ikeda D, *et al.* Addition of oral sildenafil to beraprost is a safe and effective therapeutic option for patients with pulmonary hypertension. *J Cardiovasc Pharmacol* 2005; 45: 286–9.
13. Hoeper MM, *et al.* Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004; 24: 1007–10.
14. Mathai SC, *et al.* Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. *Eur Respir J* 2007; 29: 469–75.
15. Hoeper MM, Welte T. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006; 354: 1091.
16. Galiè N, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006; 354: 1092–3.
17. Hemnes AR, Robbins IM. Sildenafil monotherapy in portopulmonary hypertension can facilitate liver transplantation. *Liver Transpl* 2009; 15: 15–19.
18. Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 18/01/08).
19. Leibovitch L, *et al.* Therapeutic applications of sildenafil citrate in the management of paediatric pulmonary hypertension. *Drugs* 2007; 67: 57–73.
20. Huddleston AJ, *et al.* Sildenafil for the treatment of pulmonary hypertension in pediatric patients. *Pediatr Cardiol* 2009; 30: 871–82.
21. Mourani PM, *et al.* Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. *J Pediatr* 2009; 154: 379–84.
22. Aldashev AA, *et al.* Phosphodiesterase type 5 and high altitude pulmonary hypertension. *Thorax* 2005; 60: 683–7.
23. Suntharalingam J, *et al.* Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2008; 134: 229–36.

Raynaud's syndrome. Sildenafil has been reported to be of benefit in Raynaud's phenomenon (see Vasospastic Arterial Disorders, p. 1275.3) resistant to vasodilator therapy.[1]

1. Pries R, *et al.* Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation* 2005; 112: 2980–5.

Adverse Effects

Adverse effects most commonly reported with sildenafil are headache, flushing, and dyspepsia. Also common are visual disturbances such as blurred vision, photophobia, chromatopsia, cyanopsia, eye irritation, pain and redness of the eyes. Retinal haemorrhage has occurred, and non-arteritic anterior ischaemic optic neuropathy (NAION) causing permanent loss of vision has been reported rarely. Other common adverse effects include dizziness, insomnia, anxiety, vertigo, epistaxis, nasal congestion, pyrexia, and gastrointestinal disturbances such as diarrhoea and vomiting. Priapism can occur.

Other adverse effects include skin rashes, erythema, alopecia, limb and/or back pain, myalgia, facial oedema, fluid retention, paraesthesia, and urinary-tract infection. Dyspnoea, cough, rhinitis, sinusitis, bronchitis, and cellulitis can occur. Sudden decrease or loss of hearing has been reported. Other reported effects include anaemia, leucopenia, gynaecomastia, urinary frequency or incontinence, haematuria, and seizures. Hypersensitivity reactions have been reported rarely.

Cerebrovascular haemorrhage and transient ischaemic attacks have occurred. There have also been reports of palpitations, syncope, hypertension, hypotension, and serious cardiovascular events including myocardial infarction, arrhythmias, tachycardia, unstable angina, and sudden cardiac death.

Reviews.

1. Vitezic D. A risk-benefit assessment of sildenafil in the treatment of erectile dysfunction. *Drug Safety* 2001; 24: 255–65.
2. Padma-nathan H, *et al.* A 4-year update on the safety of sildenafil citrate (Viagra). *Urology* 2002; 60 (suppl 2): 67–90.
3. Tsertsvadze A, *et al.* Oral sildenafil citrate (Viagra) for erectile dysfunction: a systematic review and meta-analysis of harms. *Urology* 2009; 74: 831–836.

Convulsions. A report[1] of 2 patients who had a first tonic-clonic seizure shortly after taking sildenafil.

1. Gilad R, *et al.* Tonic-clonic seizures in patients taking sildenafil. *BMJ* 2002; 325: 869.

Effects on the blood. Thrombocytopenia has been reported in a patient taking sildenafil 25 mg three times daily. The patient's platelet count increased when sildenafil was stopped and decreased on rechallenge.[1]

1. Philip A, *et al.* Sildenafil-induced thrombocytopenia. *Ann Intern Med* 2008; 149: 437–9.

Effects on the cardiovascular system. The effects of phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, and vardenafil) on the cardiovascular system,[1,2] and the potential risks of sexual activity in men with cardiovascular disease,[3] have been reviewed.

There has been considerable uncertainty about the potential cardiovascular risk associated with sildenafil treatment. Minor effects associated with vasodilatation, such as headache and flushing are relatively common, but in patients without pre-existing cardiovascular risk factors the risk of serious cardiovascular events associated with the drug appears to be low. However, there have been reports of myocardial infarction in patients who had no apparent risk factors,[4,5] and a consensus document issued by the American College of Cardiology and the American Heart Association (ACC/AHA) has pointed out that patients with erectile dysfunction are mostly over 45 years of age and are more likely to have risk factors predisposing them to cardiovascular disease.[6]

As of November 1998, 130 deaths in US patients taking sildenafil had been reported to the FDA; 3 of these were due to stroke and 77 to some other cardiovascular event.[7] The nature of the relationship between drug and event was considered unclear, but some of these patients were also receiving nitrates, a combination now contra-indicated because of the greatly increased risk of potentially life-threatening hypotension.[6] The Australian Adverse Drug Reactions Advisory Committee[8] stated in June 2002 that it had received 773 reports of adverse reactions associated with the use of sildenafil. There were 20 reports of myocardial infarction, including 4 fatalities; 9 of these 20 patients had pre-existing cardiovascular disease or diabetes or were considered to be at high risk of cardiovascular disease, and 1 patient was taking nitrates. Other cardiovascular effects reported included 26 reports of chest pain and 10 other fatalities (6 sudden unexplained deaths, 2 strokes, and 2 subarachnoid haemorrhages). However, it was pointed out that the timing of these adverse effects in relation to sildenafil ingestion was often not reported and that, since sildenafil is taken in the context of sexual activity and, in some cases, underlying coronary disease, the contribution of sildenafil to cardiac events was difficult to assess.

It is still uncertain whether patients with **pre-existing** cardiovascular disease are at increased risk when taking sildenafil without concomitant nitrates. The ACC/AHA consensus statement noted that the evidence was scanty and suggested that sildenafil could be used, but with caution, in patients with stable *coronary artery disease* provided that nitrates were not taken.[6] A later review[9] and studies using exercise testing[10,11] also concluded that sildenafil appeared to be well tolerated in most patients with chronic stable coronary artery disease. In men with mild to moderate chronic *heart failure*, small studies have found that sildenafil was well tolerated and effective for erectile dysfunction,[12-14] and improved measures of exercise capacity.[12] Analyses[15,16] of combined study data have examined the effects of sildenafil in men stabilised on antihypertensive treatment (including diuretics, beta blockers, alpha blockers, ACE inhibitors, and calcium-channel blockers) compared with men who did not have *hypertension*. Similar results were found for both groups in terms of sildenafil's efficacy for erectile dysfunction.[16] Also, changes in blood pressure and heart rate after a dose of sildenafil,[15] and the incidence of treatment-related adverse effects that were potentially related to blood pressure decrease,[16] were not significantly different between the groups. Evidence to assess the risk in other cardiovascular disorders is less extensive, although a case report of a patient with hypertrophic *cardiomyopathy* who had cardiovascular adverse effects after a dose of sildenafil suggested that the drug may precipitate an unstable haemodynamic state in this condition.[17]

1. Brindis RG, Kloner RA. Sildenafil in patients with cardiovascular disease. *Am J Cardiol* 2003; 92 (suppl): 26M–36M.
2. Kloner RA. Cardiovascular effects of the 3 phosphodiesterase-5 inhibitors approved for the treatment of erectile dysfunction. *Circulation* 2004; 110: 3149–55.
3. Kostis JB, *et al.* Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005; 96: 313–21.
4. Peenstra J, *et al.* Acute myocardial infarction associated with sildenafil. *Lancet* 1998; 352: 957–8.
5. Kekilli M, *et al.* Acute myocardial infarction after sildenafil citrate ingestion. *Ann Pharmacother* 2005; 39: 1362–4.
6. Cheitlin MD, *et al.* Use of sildenafil (Viagra) in patients with cardiovascular disease. ACC/AHA Expert Consensus Document. *J Am Coll Cardiol* 1999; 33: 273–82. Correction. *ibid.*; 34: 1850. Also available at: http://circ.ahajournals.org/cgi/reprint/99/1/168.pdf (accessed 29/11/05)
7. FDA. Postmarketing safety of sildenafil citrate (Viagra): summary of reports of death in Viagra users received from marketing (late March) through mid-November 1998. Available at: http://www.fda.gov/cder/consumerinfo/viagra/safety3.htm (accessed 29/11/05)
8. Adverse Drug Reactions Advisory Committee (ADRAC). Sildenafil—three years experience. *Aust Adverse Drug React Bull* 2002; 21: 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 02/09/08)
9. Tran D, Howes LG. Cardiovascular safety of sildenafil. *Drug Safety* 2003; 26: 453–60.
10. Arruda-Olson AM, *et al.* Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease: a randomized crossover trial. *JAMA* 2002; 287: 719–25.
11. Fox KM, *et al.* Sildenafil citrate does not reduce exercise tolerance in men with erectile dysfunction and chronic stable angina. *Eur Heart J* 2003; 24: 2206–12.
12. Bocchi EA, *et al.* Sildenafil effects on exercise, neurohormonal activation, and erectile dysfunction in congestive heart failure: a double-blind, placebo-controlled, randomized study followed by a prospective treatment for erectile dysfunction. *Circulation* 2002; 106: 1097–1103.
13. Webster LJ, *et al.* Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-

controlled, double-blind crossover trial. *Arch Intern Med* 2004; 164: 514–20.
14. Katz SD, *et al.* Efficacy and safety of sildenafil citrate in men with erectile dysfunction and chronic heart failure. *Am J Cardiol* 2005; 95: 36–42.
15. Zusman RM, *et al.* Effect of sildenafil citrate on blood pressure and heart rate in men with erectile dysfunction taking concomitant antihypertensive medication. *J Hypertens* 2000; 18: 1865–9.
16. Kloner RA, *et al.* Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. *Am J Hypertens* 2001; 14: 70–3.
17. Stauffer J-C, *et al.* Subaortic obstruction after sildenafil in a patient with hypertrophic cardiomyopathy. *N Engl J Med* 1999; 341: 700–701.

Effects on the ears. As of October 2007, the US FDA had received a total of 29 postmarketing reports of sudden hearing loss with phosphodiesterase type-5 inhibitors. The problem was sometimes accompanied by tinnitus, vertigo, or dizziness. In most of the cases, the hearing loss involved one ear, and it was either a partial or complete loss of hearing. In about one-third of cases, the loss was temporary. While a causal relationship could not be established, patients should be advised that hearing loss may be related to these drugs, and to seek medical attention if affected.[1]

1. FDA. FDA announces revisions to labels for Cialis, Levitra and Viagra: potential risk of sudden hearing loss with ED drugs to be displayed more prominently (issued 18th October 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01730.html (accessed 18/01/08)

Effects on the eyes. The Australian Adverse Drug Reactions Advisory Committee[1] stated in June 2002 that it had received 65 reports of abnormal vision from a total of 773 adverse reactions associated with use of sildenafil reported over 3 years. A bluish tinge or haze to vision and some increased light sensitivity has been reported by patients taking sildenafil, with the percentage of reports increasing with increasing dose.[2] The visual symptoms usually peak 1 to 2 hours after ingestion and resolve about 3 to 4 hours later. The effects of a single dose of sildenafil 100 mg were studied in 5 healthy subjects.[3] Electroretinogram measurements showed significant changes that correlated well with plasma-sildenafil concentrations, peaking at 1 hour after administration and showing complete recovery at the 6-hour measurements. Inhibition of phosphodiesterase type-6 in rod photoreceptors is the most likely mechanism of sildenafil-associated retinal dysfunction. A review of visual disorders associated with 5-phosphodiesterase inhibitors noted that pooled reports of disturbances of vision with sildenafil suggest an incidence of 2 to 5%; the frequency with vardenafil and tadalafil seems to be lower although the evidence is limited. There is also little evidence of retinal toxicity, but this class of drugs is not recommended for use in patients with hereditary degenerative retinal disorders since they have minor inhibitory effects on 6-phosphodiesterase which has an important role in the visual transduction cascade.[4]

Other visual disturbances reported in patients taking sildenafil have included temporary loss of vision and increased intra-ocular pressure.[5] A 69-year-old man who had permanent loss of vision in one eye a few hours after taking sildenafil 100 mg was found to have an occlusion in a retinal artery.[6] In another similar case of retinal artery occlusion[7] the patient also had uncontrolled hypertension; the authors suggested that embolisation by a pre-existing arteriosclerotic plaque of the carotid artery resulted from elevated blood pressure and cardiac workload during sexual activity, rather than as a direct adverse effect of sildenafil.

Several cases of persistent blurred vision and visual loss caused by nonarteritic anterior ischaemic optic neuropathy (NAION; vascular insufficiency and ischaemia at the optic nerve head) associated with sildenafil use have been reported.[8-11] Generally, visual defects developed in one eye only within 24 hours of sildenafil ingestion, although many of these men had taken doses of sildenafil on past occasions without adverse effect. A small number of cases have also been reported for tadalafil[11-14] and vardenafil.[11] However, many of these men had underlying anatomic or vascular risk factors for NAION, including low cup to disc ratio (crowded disc), age over 50, diabetes, hypertension, ischaemic heart disease, hyperlipidaemia, and smoking. A small, retrospective, case-control study suggested that men who use sildenafil or tadalafil and have a history of myocardial infarction may be at an increased risk of NAION.[15] As of May 2005 the FDA had concluded that it was not possible to determine whether NAION was directly related to the use of phosphodiesterase type-5 inhibitors, the patients' underlying vascular risk factors or anatomical defects, a combination of these factors, or other factors.[11] Later reviews came to similar conclusions,[4,16] and the estimated incidence of NAION in men receiving sildenafil has been calculated to be similar to estimates for the general population.[17]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Sildenafil—three years experience. *Aust Adverse Drug React Bull* 2002; 21: 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 02/09/08)
2. Marmor MF. Sildenafil (Viagra) and ophthalmology. *Arch Ophthalmol* 1999; 117: 518–19.
3. Vobig MA, *et al.* Retinal side-effects of sildenafil. *Lancet* 1999; 353: 375.
4. Laties AM. Vision disorders and phosphodiesterase type 5 inhibitors: a review of the evidence to date. *Drug Safety* 2009; 32: 1–18.
5. CSM/MCA Sildenafil (Viagra). *Current Problems* 1999; 25: 16. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 02/09/08)
6. Tripathi A, O'Donnell N. Branch retinal artery occlusion: another complication of sildenafil. *Br J Ophthalmol* 2000; 84: 934–5.
7. Bertoluci A, *et al.* Hemi-retinal artery occlusion associated with sexual activity and sildenafil citrate (Viagra). *Acta Ophthalmol Scand* 2003; 81: 198–200.
8. Boshier A, *et al.* A case of nonarteritic ischemic optic neuropathy (NAION) in a male patient taking sildenafil. *Int J Clin Pharmacol Ther* 2002; 40: 422–3.
9. Pomeranz HD, *et al.* Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2002; 109: 584–7.
10. Pomeranz HD, Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (Viagra): a report of seven new cases. *J Neuroophthalmol* 2005; 25: 9–13.
11. FDA. Alert 07/2005: Sildenafil (marketed as Viagra). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/sildenafilHCP.pdf (accessed 28/07/05)
12. Peter NM, *et al.* Tadalafil-associated anterior ischaemic optic neuropathy. *Eye* 2005; 19: 715–17.
13. Escaravage GK, *et al.* Tadalafil associated with anterior ischemic optic neuropathy. *Arch Ophthalmol* 2005; 123: 399–400.
14. Bollinger K, Lee MS. Recurrent visual field defect and ischemic optic neuropathy associated with tadalafil rechallenge. *Arch Ophthalmol* 2005; 123: 400–401.
15. McGwin G, *et al.* Non-arteritic anterior ischaemic optic neuropathy and the treatment of erectile dysfunction. *Br J Ophthalmol* 2006; 90: 154–7.
16. Danesh-Meyer HV, Levin LA. Erectile dysfunction drugs and risk of anterior ischaemic optic neuropathy: casual or causal association? *Br J Ophthalmol* 2007; 91: 1551–5.
17. Gorkin L, *et al.* Sildenafil citrate use and the incidence of nonarteritic anterior ischemic optic neuropathy. *Int J Clin Pract* 2006; 60: 500–3.

Effects on mental function. There have been a few cases reported[1-3] of transient global amnesia after the use of sildenafil or tadalafil. Between January 1998 and February 2001, the FDA had received 35 reports of amnesia in which sildenafil was listed as the primary causal suspect.[4]

1. Gandolfo C, *et al.* Sildenafil and transient global amnesia. *Neurol Sci* 2003; 24: 145–6.
2. Savitz SA, Caplan LR. Transient global amnesia after sildenafil (Viagra) use. *Neurology* 2002; 59: 778
3. Schiefer J, Sparing R. Transient global amnesia after intake of tadalafil, a PDE-5 inhibitor: a possible association? *Int J Impot Res* 2005; 17: 383–4.
4. Milman HA, Arnold SB. Neurologic, psychological, and aggressive disturbances with sildenafil. *Ann Pharmacother* 2002; 36: 1129–34.

Precautions

Caution is required in patients with hepatic or severe renal impairment, and dosage reduction of sildenafil may be necessary. Care is also needed in patients with anatomical deformation of the penis or haematological disorders that may predispose them to priapism. In the event of prolonged erection (for more than 4 hours), patients should seek medical assistance, as penile tissue damage and permanent loss of potency can occur. Patients are also advised to stop taking sildenafil and seek medical advice in cases of sudden visual or hearing loss. Sildenafil should not be given to those with loss of vision in one eye caused by non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this was in connection with previous phosphodiesterase type-5 inhibitors or not. Patients who experience dizziness or visual disturbances should not drive or operate hazardous machinery.

The safety of sildenafil is uncertain in patients with severe hepatic impairment, bleeding disorders, active peptic ulceration, hypotension, hypertension, a recent history of stroke, myocardial infarction, or life-threatening arrhythmia, unstable angina, heart failure, or retinal disorders such as retinitis pigmentosa (a minority of whom have genetic disorders of retinal phosphodiesterases). Licensed product information advises that it should not be used in these groups.

Cardiovascular disease. For mention of a consensus statement on the use of sildenafil in patients with cardiovascular disease, see p. 2365.2.

Contamination of herbal preparations. Sildenafil has been found in products marketed as dietary supplements or "herbal Viagra" for erectile dysfunction. Serious adverse effects have been reported and the FDA issued a warning highlighting the potential for interactions with prescription medication. Other drugs that have been identified as contaminants of such herbal preparations include glibenclamide and tadalafil.[1]

For mention of drugs related to sildenafil that have been used similarly in dietary supplements, see Acetildenafil p. 2351.3.

1. MHRA/CHM. Herbal products marketed for erectile dysfunction. *Drug Safety Update* 2008; 1(11): 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0179306&RevisionSelectionMethod=LatestReleased (accessed 13/11/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sildenafil 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

Sildenafil or other phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contra-indicated in patients receiving such drugs. Volatile nitrates and sodium nitroprusside will be similarly affected. Sildenafil may also enhance the hypotensive effect of nicorandil and use of the two drugs together should be avoided. Symptomatic hypotension may also occur when phosphodiesterase type-5 inhibitors are given with alpha blockers. Generally, the patient should be stabilised on alpha blocker therapy before the phosphodiesterase type-5 inhibitor is started at a low dose and adjusted according to response. Drugs that inhibit the cytochrome P450 isoenzyme CYP3A4, such as cimetidine, delavirdine, erythromycin, itraconazole, and ketoconazole, may reduce the clearance of phosphodiesterase type-5 inhibitors, necessitating a reduction in dosage. Plasma concentrations of phosphodiesterase type-5 inhibitors are significantly increased by HIV-protease inhibitors, and particularly so by ritonavir-boosted regimens. Such combinations should not be given unless absolutely essential. Grapefruit juice should be avoided with sildenafil or other phosphodiesterase type-5 inhibitors as it may increase their plasma concentrations. Inducers of CYP3A4, such as rifampicin, are likely to decrease plasma concentrations of phosphodiesterase type-5 inhibitors. Bosentan also reduces exposure to sildenafil.

Specific dosage recommendations have been made for the use of phosphodiesterase type-5 inhibitors with many of these drugs; see Uses and Administration under Avanafil (p. 2354.1), Sildenafil (p. 2364.2), Tadalafil (p. 2368.2), and Vardenafil (p. 2372.1).

Antivirals. Rises in sildenafil concentrations after use of *saquinavir* or *ritonavir* were consistent[1] with inhibition of metabolism mediated by the cytochrome P450 isoenzyme CYP3A4. The larger increases seen with ritonavir may be due to its additional inhibition of the isoenzyme CYP2C9. Fatal myocardial infarction has been reported[2] in a 47-year-old patient who took sildenafil 25 mg with ritonavir and saquinavir. In a study[3] of 6 HIV-positive men being treated with triple antiretroviral therapy that included *indinavir*, plasma concentrations of sildenafil were found to be significantly increased compared with historical controls.

1. Muirhead GJ, *et al.* Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *Br J Pharmacol* 2000; 50: 99–107.
2. Hall MCS, Ahmad S. Interaction between sildenafil and HIV-1 combination therapy. *Lancet* 1999; 353: 2071–2.
3. Merry C, *et al.* Interaction of sildenafil and indinavir when co-administered to HIV-positive patients. *AIDS* 1999; 13: F101–F107.

Cardiovascular drugs. For the effects of sildenafil in men stabilised on *antihypertensives* in general, see Effects on the Cardiovascular System, p. 2365.2. For mention of a possible interaction between sildenafil and *verapamil*, see Immunosuppressants, p. 2367.1.

A two-way interaction appears to exist between sildenafil and *bosentan*. In a placebo-controlled study[1] in 55 healthy subjects plasma concentrations of bosentan increased when taken with sildenafil, while those of sildenafil decreased. The combination was well tolerated however, and the clinical significance of the interaction was not clear.

In men with stable angina given sildenafil and sublingual *glyceryl trinitrate*, hypotensive symptoms occurred for at least 8 hours after dosing; the interaction was not considered synergistic after 6 hours, although there were still additive effects on blood pressure. The authors suggested that this data might support the cautious use of glyceryl trinitrate in patients hospitalised for angina who were haemodynamically stable but had taken sildenafil at least 6 hours previously.[2]

1. Burgess G, *et al.* Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. *Eur J Clin Pharmacol* 2008; 64: 43–50.
2. Oliver JJ, *et al.* Time-dependent interactions of the hypotensive effects of sildenafil citrate and sublingual glyceryl trinitrate. *Br J Clin Pharmacol* 2009; 67: 403–12.

Dihydrocodeine. The use of dihydrocodeine with sildenafil was associated with priapism in 2 men who had previously been treated successfully with sildenafil.[1] The first patient had two prolonged erections, lasting 4 and 5 hours, and the effect did not recur when the dihydrocodeine was stopped. The second patient had priapism on 3 occasions in the first week of dihydrocodeine treatment, but not in the subsequent 2 weeks despite continuing both drugs.

1. Goldmeier D, Lamba H. Prolonged erections produced by dihydrocodeine and sildenafil. *BMJ* 2002; 324: 1555.

Food. *Grapefruit juice* has been shown to increase bioavailability but delay absorption of sildenafil in healthy subjects.[1]

1. Jetter A, *et al.* Effects of grapefruit juice on the pharmacokinetics of sildenafil. *Clin Pharmacol Ther* 2002; 71: 21–9.

Immunosuppressants. Studies in men with erectile dysfunction who were receiving *tacrolimus* after kidney transplantation found that sildenafil had no effect on tacrolimus pharmacokinetics.[1,2] However, the pharmacokinetic profile of sildenafil differed from that reported in healthy subjects; the maximal plasma concentration was higher, the area under the concentration-time curve was increased, and the elimination half-life was prolonged.[1] Reductions in blood pressure were also found when sildenafil was given, although this may have been due to an interaction with *verapamil*. The authors suggested that an initial dose of 25 mg sildenafil should be used, and that on the days of sildenafil use the doses of antihypertensive drugs may need to be adjusted according to blood pressure response.[1,2]

1. Christ B, *et al.* Interactions of sildenafil and tacrolimus in men with erectile dysfunction after kidney transplantation. *Urology* 2001; 58: 589–93.
2. Christ B, *et al.* Investigation on interaction between tacrolimus and sildenafil in kidney-transplanted patients with erectile dysfunction. *Int J Clin Pharmacol Ther* 2004; 42: 149–56.

Nitrates. Giving sildenafil 50 mg to patients receiving *isosorbide mononitrate*, or sublingual *glyceryl trinitrate* given 1 hour after sildenafil, resulted in substantially greater decreases in blood pressure than when the nitrate was given alone in 2 crossover studies in patients with angina.[1] Treatment-related adverse effects were reported in 8 of 16 patients who received sildenafil with isosorbide mononitrate and 3 of 15 who took sildenafil with glyceryl trinitrate. The authors confirmed that sildenafil should not be taken with nitrates.

1. Webb DJ, *et al.* Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000; 36: 25–31.

Pharmacokinetics

Sildenafil is rapidly absorbed after an oral dose, with a bioavailability of about 40%. Peak plasma concentrations occur within 30 to 120 minutes; the rate of absorption is reduced when sildenafil is given with food.

Sildenafil is widely distributed into tissues and is about 96% bound to plasma proteins. It is metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 (the major route) and CYP2C9. The major metabolite, *N*-desmethylsildenafil (UK-103320) also has some activity. The terminal half-lives of sildenafil and the *N*-desmethyl metabolite are about 4 hours.

Sildenafil is excreted as metabolites, mainly in the faeces, and to a lesser extent the urine. Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

References.

1. Nichols DJ, *et al.* Pharmacokinetics of sildenafil citrate after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol* 2002; 53 (suppl 1): 5S–12S.
2. Muirhead GJ, *et al.* The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil. *Br J Clin Pharmacol* 2002; 53 (suppl 1): 21S–30S.
3. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; 45: 987–1003.
4. Mukherjee A, *et al.* Population pharmacokinetics of sildenafil in term neonates: evidence of rapid maturation of metabolic clearance in the early postnatal period. *Clin Pharmacol Ther* 2009; 85: 56–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Activil; Almaximo; Anaus; Bifort; Cagno; Egomax; Erectol; Expit; Falic; File; Firmel; Forzak; Gimonte Sildenafil; Gladium; Hepil; Incresil; Juvigor; Labsamax; *Lorbinafil*; *Lumix*; *Magnus*; *Maxdosa*; *Maximo*†; Nexofil†; Nitro; Openvas; Paramen; Permitil; Pluspen; Segurex; Sildefil†; Super-O; Tecnomax; Viagra; Vigor Plus; Vimax; Virilon; Viripotens; Vorst; *Austral.*: Revatio; Viagra; *Austria*: Revatio; Viagra; *Belg.*: Revatio; Viagra; *Braz.*: Dejavu; Escitan; Revatio; Sollevare; Tantrix; Vasifil; Viagra; Virineo; *Canad.*: Revatio; Viagra; *Chile*: Alfin; Dirtop; Disilden; Erosfil; Esantop; Helpin; Lifter; Novalif; Plusefec; Ripol; Selert†; Selerup; Siafil; Viagra; Vigorex; Vimax; Zilfic; *China*: Viagra (万艾可); *Cz.*: Amfidor; Ecriten; Fildlata; Revatio; Silaxa; Silfeldrem; Viagra; Vigrande; Vizarsin; *Denm.*: Revatio; Viagra; *Fin.*: Viagra; *Fr.*: Revatio; Viagra; *Ger.*: Revatio; Viagra; *Gr.*: Revatio; Viagra; *Hong Kong*: Revatio; Viagra; *Hung.*: Revatio; Viagra; *India*: Adams Delite; Air Bus; Alsigra; Androz; Be-Force; Bison; C-Gra; Caverta; Echarge; Edegra; Enthusia; Erec; Erectimax; Funtoosh; Hewon; Honygra; Intagra; Integra; Jean Siagra; Josh-IN; Juan; Kamagra; Leegra; Lovegra; Lupigra; Manforce; Manpower; Meriday; Moragara; N-Gra; Neogra; Niagra; Nyte; Penegra; Silagra; Viagra; *Indon.*: Viagra; Vimax; *Irl.*: Revatio; Sidena; Viagra; Vizarsin; *Israel*: Revatio; Slider; Tarim; Via-Avenir; Viagra; *Ital.*: Revatio; Viagra; *Jpn*: Viagra; *Malaysia*: Viagra; *Mex.*: Apodefil; Patrex; Viagra; *Neth.*: Afilon; Arifil; Azulsix; Enafilzil; Fildlata; Revatio; Silden; Sildenamed; Silderec; Sildrem; Silfeldrem; Tornetis; Viagra; Vilgendra; Vizarsin; *Norw.*: Revatio; Viagra; *NZ*: Avigra; Revatio; Silvasta; Vedafil; Viagra; *Philipp.*: Adonix; Ambigra; Andros; Brefil; Neo-Up; Viagra; Zilden; *Pol.*: Ecriten; Falsigra; Maxigra; Revatio; Viagra; Vigrande; Vizarsin; *Port.*: Revatio; Viagra; *Rus.*: Viagra (Виагра); Viasan-LF (Виасан-ЛФ); *S.Afr.*: Avigra; Viagra; *Singapore*: Revatio; Viagra; *Spain*: Dragul; Oximum; Revatio; Viagra; Vizarsin; *Swed.*: Revatio; Viagra; *Switz.*: Revatio; Viagra; *Thai.*: Elonza; Revatio; Sildegra; Viagra; *Turk.*: Degra; Egira; Revatio; Sildegra; Viagra; Vigrande; *UK*: Nipatra; Revatio; Viagra; Vizarsin; *Ukr.*: Conegra (Конегра); Erasmo (Эрасмо)†; Erektil (Эректил); Eroton (Эротон); Extra (Экстра)†; Intagra (Интагра); Novygra (Новигра); Penimex (Пенимекс); Potentiale (Потенциале); Silada (Силада); Superviga (Супервига); Ulti-mate (Алти-Мет); Vecta (Векта)†; Viagra (Виагра); Vigrande (Вигранде); *USA*: Revatio; Viagra; *Venez.*: Duroval; Itaka; Viagra; Viasek; Viasil; Vigrasol; Viosex; Viridil.

Pharmacopoeial Preparations

USP 36: Sildenafil Citrate Oral Suspension.

Silodosin *(BAN, rINN)*

KAD-3213; KMD-3213; Selodosin; Silodosina; Silodosine; Silodosinum; Сильодозин.

(-)-1-(3-Hydroxypropyl)-5-[(2*R*)-2-([2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino)propyl]-2,3-dihydro-1*H*-indole-7-carboxamide.

$C_{25}H_{32}F_3N_3O_4$=495.5

CAS — 160970-54-7.

ATC — G04CA04.

ATC Vet — QG04CA04.

UNII — CUZ39LUY82.

Uses and Administration

Silodosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) that is reported to be selective for the alpha$_{1A}$-adrenoceptor subtype. It is used orally in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction, in a usual dose of 8 mg daily with food, as a single dose or in 2 divided doses. Doses may need to be reduced in renal impairment, see below.

References.

1. Schiltz S, Benzeroual KE. Silodosin: a selective α_{1A}-adrenergic receptor antagonist for the treatment of benign prostatic hyperplasia. *Clin Ther* 2009; 31: 2489–2502.
2. Cantrell MA, *et al.* Silodosin for benign prostatic hyperplasia. *Ann Pharmacother* 2010; 44: 302–10.

Administration in renal impairment. Exposure to silodosin may be increased in patients with renal impairment. No dosage adjustment is considered necessary in patients with mild renal impairment (creatinine clearance, CC, 50 mL/minute and above). In those with moderate renal impairment (CC 30 to 50 mL/minute), the oral dose should be reduced to 4 mg once daily; silodosin is contra-indicated in severe impairment (CC less than 30 mL/minute).

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3 and p. 1475.1. Additional adverse effects include ejaculation abnormalities such as retrograde ejaculation (reversible on stopping treatment), arrhythmias, increased blood triglycerides, and skin reactions. Intraoperative floppy iris syndrome has also been associated with the use of alpha blockers, see Cataract Surgery, under Tamsulosin p. 2369.3.

Silodosin should not be used in patients with severe renal impairment, and the dose may need to be adjusted in those with moderate renal impairment (see Administration in Renal Impairment, above). Increases in liver enzyme values, impaired hepatic function, and jaundice have been reported; silodosin should be avoided in patients with severe hepatic impairment. It should also not be used with strong inhibitors of cytochrome P450 isoenzyme CYP3A4 or P-glycoprotein; caution is required when used with moderate CYP3A4 inhibitors (see Interactions, below).

Interactions

As for Prazosin Hydrochloride, p. 1475.1.

Silodosin is metabolised by the cytochrome P450 isoenzyme CYP3A4, and use with CYP3A4 inhibitors may increase exposure to silodosin. Use with strong CYP3A4 inhibitors such as ketoconazole is contra-indicated; caution is advised with use of moderate CYP3A4 inhibitors. Silodosin is also metabolised by UDP-glucuronosyltransferase 2B7 (UGT2B7), and use with inhibitors of this enzyme may increase silodosin exposure.

Silodosin is a P-glycoprotein substrate, and use with P-glycoprotein inhibitors may increase exposure to silodosin; use with strong inhibitors such as ciclosporin is not recommended.

Pharmacokinetics

Peak concentrations of silodosin occur about 2.6 hours after an oral dose; absolute bioavailability is about 32%. Exposure to silodosin is decreased when given with a meal that is moderately high in fat and calories. Silodosin is about 97% protein bound. It undergoes extensive metabolism through glucuronidation, alcohol and aldehyde dehydrogenase, and cytochrome P450 isoenzyme CYP3A4. The main metabolite is a glucuronide conjugate (KMD-3213G) that is formed via UDP-glucuronosyltransferase 2B7; it is active and has a half-life of about 24 hours, with a four times greater exposure than silodosin. The second major metabolite (KMD-3293) is formed by alcohol and aldehyde dehydrogenase; it is not expected to contribute to the overall activity. After oral dosing, about 34% is recovered in the urine and 55% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Silodyx; *Canad.*: Rapaflo; *Cz.*: Silodyx; Urorec; *Fr.*: Silodyx; Urorec; *Ger.*: Urorec; *Gr.*: Silodyx; Urorec; *Irl.*: Silodyx; Urorec; *Jpn*: Uriel; *Neth.*: Silodyx; Urorec; *Pol.*: Silodyx; Urorec; *Port.*: Silodyx; Urorec; *Rus.*: Urorec (Уропех); *Spain*: Silodyx; Urorec; *Ukr.*: Urorec (Уропех); *USA*: Rapaflo.

Solifenacin Succinate

(BANM, USAN, rINNM)

Soliférnacine, Succinate de; Solifenacini Succinas; Succinato de solifenacina; YM-905; YM-67905; Солифенацина Сукцинат.

(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate compound with butanedioic acid (1:1).

$C_{23}H_{26}N_2O_2.C_4H_6O_4$=480.6

CAS — 242478-37-1 (solifenacin); 242478-38-2 (solifenacin succinate).

ATC — G04BD08.

ATC Vet — QG04BD08.

UNII — KKA5DLD701.

Uses and Administration

Solifenacin succinate is a selective M_3 antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used in the treatment of urinary frequency, urgency, and incontinence in detrusor instability (p. 2349.2). Solifenacin succinate is given orally in usual doses of 5 mg once daily, increased to 10 mg once daily if required. Maximum doses of 5 mg once daily are recommended in patients receiving drugs such as ketoconazole or ritonavir that are strong inhibitors of the cytochrome P450 isoenzyme CYP3A4. For doses in hepatic or renal impairment, see below.

References.

1. Chapple CR, *et al.* Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU Int* 2004; 93: 303–10.
2. Cardozo L, *et al.* Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol (Baltimore)* 2004; 172: 1919–24.
3. Haab F, *et al.* Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. *Eur Urol* 2005; 47: 376–84.
4. Chapple CR, *et al.* A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* 2005; 48: 464–70.
5. Abrams P, Swift S. Solifenacin is effective for the treatment of OAB dry patients: a pooled analysis. *Eur Urol* 2005; 48: 483–7.
6. Payne CK. Solifenacin in overactive bladder syndrome. *Drugs* 2006; 66: 175–90.
7. Garely AD, *et al.* Solifenacin for overactive bladder with incontinence: symptom bother and health-related quality of life outcomes. *Ann Pharmacother* 2007; 41: 391–8.
8. Michel MC, *et al.* Cardiovascular safety and overall tolerability of solifenacin in routine clinical use: a 12-week, open-label, post-marketing surveillance study. *Drug Safety* 2008; 31: 505–14.
9. Pelman RS, *et al.* Solifenacin at 3 years: a review of efficacy and safety. *Postgrad Med* 2008; 120: 85–91.
10. Cardozo L, *et al.* SUNRISE Study Group. Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. *BJU Int* 2008; 102: 1120–7.

Administration in hepatic and renal impairment. Oral doses of 5 mg of solifenacin succinate once daily are recommended in patients with moderate hepatic impairment (Child-Pugh category B) or severe renal impairment (creatinine clearance less than 30 mL/minute). It should not be used in patients with severe hepatic impairment (Child-Pugh category C) or in those undergoing haemodialysis.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Solifenacin succinate should be used with caution in patients also receiving inhibitors of the cytochrome P450 isoenzyme CYP3A4 (see Interactions, p. 2368.1 and Uses and Administration, above). It should also be used with caution in hepatic and renal impairment.

Effects on the cardiovascular system. A 12-week post-marketing surveillance study found solifenacin had no

effect on the heart rate or blood pressure of patients with overactive bladder syndrome, despite many patients having cardiovascular co-morbidities.[1] However, US licensed product information states that QT prolongation and torsade de pointes have been reported in association with solifenacin use, although causality and frequency could not be determined.

1. Michel MC, *et al.* Cardiovascular safety and overall tolerability of solifenacin in routine clinical use: a 12-week, open-label, post-marketing surveillance study. *Drug Safety* 2008; 31: 505–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies solifenacin 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

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Exposure to solifenacin succinate may be increased by drugs that inhibit the cytochrome P450 isoenzyme CYP3A4. Although there is a lack of data, licensed product information also warns of the potential for interaction between solifenacin succinate and substrates or inducers of CYP3A4. Dosage adjustment for solifenacin succinate may be necessary (see Uses and Administration, p. 2367.3).

Pharmacokinetics

After an oral dose, solifenacin succinate is absorbed from the gastrointestinal tract; peak plasma concentrations occur after 3 to 8 hours and bioavailability is about 90%. Solifenacin is about 98% bound to plasma proteins. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, and has a terminal half-life of 45 to 68 hours. Solifenacin is excreted mainly as metabolites in urine and faeces.

References.
1. Kuipers ME, *et al.* Solifenacin demonstrates high absolute bioavailability in healthy men. *Drugs R D* 2004; 5: 73–81.
2. Smulders RA, *et al.* Pharmacokinetics and safety of solifenacin succinate in healthy young men. *J Clin Pharmacol* 2004; 44: 1023–33.
3. Doroshyenko O, Fuhr U. Clinical pharmacokinetics and pharmacodynamics of solifenacin. *Clin Pharmacokinet* 2009; 48: 281–302.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Vesicare; ***Austral.***: Vesicare; ***Austria***: Vesicare; ***Belg.***: Vesicare; ***Braz.***: Vesicade; Vesicare; ***Canad.***: Vesicare; ***China***: Vesicare (卫喜康); ***Cz.***: Asolfena; Vesicare; Zevesin; ***Denm.***: Vesicare; ***Fin.***: Vesicare; ***Fr.***: Vesicare; ***Ger.***: Vesikur; ***Gr.***: Vesicare; ***Hong Kong***: Vesicare; ***Hung.***: Vesicare; ***India***: Bispec; ***Indon.***: Vesicare; ***Irl.***: Vesitirim; ***Israel***: Vesicare; ***Ital.***: Vesiker; ***Jpn***: Vesicare; ***Malaysia***: Vesicare; ***Mex.***: Vesicare; ***Neth.***: Flomin; Uriclin†; Vesicare; ***Norw.***: Vesicare; ***NZ***: Vesicare; ***Philipp.***: Vesicare; ***Pol.***: Vesicare; ***Port.***: Flomin; Uriclin; Vesicare; ***Rus.***: Vesicare (Везикар); ***S.Afr.***: Vesicare; ***Singapore***: Vesicare; ***Spain***: Vesicare; ***Swed.***: Vesicare; ***Switz.***: Vesicare; ***Thai.***: Vesicare; ***Turk.***: Kinzy; ***UK***: Vesicare; ***Ukr.***: Vesicare (Везикар); ***USA***: Vesicare.

Tadalafil *(BAN, USAN, rINN)*

GF-196960; IC-351; Tadalafiili; Tadalafila; Tadalafilo; Tadalafilum; Тадалафил.

(6*R*,12a*R*)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-[3,4-(methylenedioxy)phenyl]pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione.

$C_{22}H_{19}N_3O_4$=389.4

CAS — 171596-29-5.

ATC — G04BE08.

ATC Vet — QG04BE08.

UNII — 742SXX0ICT.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of tadalafil:

Weekend Pill.

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

Ph. Eur. 8: (Tadalafil). A white or almost white powder. Practically insoluble in water; slightly soluble in dichloromethane; freely soluble in dimethyl sulfoxide.

USP 36: (Tadalafil). A white or almost white powder. Practically insoluble in water; slightly soluble in dichloromethane; freely soluble in dimethyl sulfoxide.

An oral suspension of tadalafil extemporaneously prepared from tadalafil tablets was stable for at least 91 days when stored in amber plastic bottles at room temperature.[1]

1. Pettit RS, *et al.* Stability of an extemporaneously prepared tadalafil suspension. *Am J Health-Syst Pharm* 2012; 69: 592–4.

Uses and Administration

Tadalafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2). It is used in the management of erectile dysfunction (p. 2348.2), of benign prostatic hyperplasia (p. 2347.1), and of pulmonary arterial hypertension (p. 1278.2).

For **erectile dysfunction**, tadalafil is given orally in a usual dose of 10 mg at least 30 minutes before sexual intercourse and may be taken with or without food; the dose may be increased to 20 mg, or decreased to 5 mg, if necessary. Efficacy may persist for up to 36 hours after dosing. Tadalafil should not be taken more than once in 24 hours.

For those who respond to tadalafil when taken as needed, and anticipate frequent use (defined as at least twice weekly), a regular daily regimen may be considered suitable. In the UK the recommended dose in such patients is 5 mg once daily, taken at about the same time each day. The dose may be decreased to 2.5 mg once daily based on individual tolerability. In the USA, the recommended starting dose of tadalafil for daily use is 2.5 mg, taken at about the same time each day, which may then be increased to 5 mg, based on tolerability and efficacy. The lowest possible starting dose of tadalafil should be given if the patient is taking an alpha blocker.

For **benign prostatic hyperplasia** tadalafil is given in a dose of 5 mg daily, taken at the same time every day. Use with an alpha blocker is not recommended.

In patients taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole or ritonavir-boosted HIV-protease inhibitors, the dose of tadalafil when used *as needed* should not exceed 10 mg once every 72 hours; when used on a *regular daily basis* for erectile dysfunction, the dose should not exceed 2.5 mg.

To improve exercise ability in **pulmonary arterial hypertension**, tadalafil is given orally in a dose of 40 mg once daily. Tadalafil therapy should be stopped at least 24 hours before starting treatment with ritonavir. In patients who have been taking ritonavir for at least one week, tadalafil therapy can be started at 20 mg once daily, and increased to 40 mg once daily as tolerated. Tadalafil should be avoided in patients taking other potent inhibitors of CYP3A4 and in patients taking potent inducers of CYP3A4.

Dosage adjustments are not necessary in elderly patients; for recommendations in hepatic or renal impairment, see below.

References.
1. Brock GB, *et al.* Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol (Baltimore)* 2002; 168: 1332–6. Correction. *ibid.* 2005; 173: 664. [dosage error in abstract]
2. Brock GB. Tadalafil: a new agent for erectile dysfunction. *Can J Urol* 2003; 10 (suppl 1): 17–22.
3. Bella AJ, Brock GB. Tadalafil in the treatment of erectile dysfunction. *Curr Urol Rep* 2003; 4: 472–8.
4. Curran MP, Keating GM. Tadalafil. *Drugs* 2003; 63: 2203–12. Correction. *ibid.*; 2703.
5. Meuleman EJ. Review of tadalafil in the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2003; 4: 2049–56.
6. Padma-Nathan H. Efficacy and tolerability of tadalafil, a novel phosphodiesterase 5 inhibitor, in treatment of erectile dysfunction. *Am J Cardiol* 2003; 92 (suppl 1): 19M–25M.
7. Carson CC, *et al.* The efficacy and safety of tadalafil: an update. *BJU Int* 2004; 93: 1276–81.
8. Doggrell SA. Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. *Expert Opin Pharmacother* 2005; 6: 75–84.
9. Donatucci CF, *et al.* Efficacy and safety of tadalafil once daily: considerations for the practical application of a daily dosing option. *Curr Med Res Opin* 2008; 24: 3383–92.
10. Galiè N, *et al.* Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; 119: 2894–2903.
11. Andersson KE, *et al.* Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action. *Neurourol Urodyn* 2011; 30: 292–301.
12. Porst H, *et al.* for the LVEJ study team. Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial. *Eur Urol* 2011; 60: 1105–13.

Administration in hepatic impairment. Exposure to tadalafil in patients with mild to moderate hepatic impairment is comparable to healthy subjects when an oral dose of 10 mg is used.

When used for **erectile dysfunction** or **benign prostatic hyperplasia**, licensed product information states the following:

- mild to moderate hepatic impairment (Child-Pugh Class A or B): the maximum oral dose is 10 mg; regular daily dosing has not been extensively evaluated and caution is required
- severe hepatic impairment (Child-Pugh Class C): insufficient data are available; in the UK, caution is advised, and in the USA use in this group is not recommended

For **pulmonary arterial hypertension**, licensed product information recommends a reduced starting dose of oral tadalafil 20 mg once daily for patients with mild to moderate hepatic impairment; again, use in patients with severe hepatic impairment is not recommended.

Administration in renal impairment. The clearance of tadalafil is reduced in renal impairment.

When used for **erectile dysfunction**, UK licensed product information for tadalafil recommends the following:

- mild to moderate renal impairment: no dose adjustment
- severe renal impairment: the maximum oral dose is 10 mg; regular daily dosing is not recommended in these patients

Dose recommendations in the USA for erectile dysfunction, when used *as needed*, in patients with renal impairment based on creatinine clearance (CC) are:

- mild (CC 51 to 80 mL/minute): no dose adjustment
- moderate (CC 30 to 50 mL/minute): an initial oral dose of 5 mg not more than once daily, with a maximum dose of 10 mg in 48 hours
- severe (CC less than 30 mL/minute or on haemodialysis): a maximum oral dose of 5 mg not more than once in every 72 hours

For patients taking tadalafil on a *regular daily basis* for erectile dysfunction only:

- mild or moderate (CC 30 mL/minute and over): no dosage adjustment
- severe (CC less than 30 mL/minute or on haemodialysis): not recommended

For patients taking tadalafil on a *regular daily basis* for **benign prostatic hyperplasia** (with or without erectile dysfunction):

- moderate (CC 30 to 50 mL/minute): an initial oral dose of 2.5 mg once daily, increased to 5 mg once daily if necessary according to response
- severe (CC less than 30 mL/minute or on haemodialysis): not recommended

In **pulmonary arterial hypertension**, a starting dose of 20 mg orally once daily is recommended in patients with mild to moderate renal impairment (CC 31 to 80 mL/minute), increased to 40 mg once daily as tolerated. Due to a lack of clinical experience, use should be avoided in patients with severe renal impairment (CC less than 30 mL/minute) or those on haemodialysis; tadalafil is not eliminated by dialysis.

High-altitude disorders. Hypoxic pulmonary hypertension associated with high altitude (p. 1276.2) may respond to tadalafil. A small study[1] has shown some promising results in adults with a history of high-altitude pulmonary oedema.

1. Maggiorini M, *et al.* Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann Intern Med* 2006; 145: 497–506.

Adverse Effects and Precautions

As for Sildenafil, p. 2365.2 and p. 2366.2. Visual disturbances may occur less frequently with tadalafil than with sildenafil. Dosage reductions may be required in patients with hepatic or renal impairment.

References.
1. Montorsi F, *et al.* Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. *Eur Urol* 2004; 45: 339–44.

Contamination of herbal preparations. For mention of dietary supplements contaminated with drugs such as tadalafil, see Contamination of Herbal Preparations, under Sildenafil p. 2366.2.

Effects on the cardiovascular system. References.
1. Kloner RA, *et al.* Cardiovascular effects of tadalafil. *Am J Cardiol* 2003; 92: 37M–46M.

Effects on the cerebrovascular system. Intracerebral haemorrhage[1] and subarachnoid haemorrhage[2] have been reported following single oral doses of tadalafil (40 mg and 20 mg, respectively) for erectile dysfunction.

1. Gazzeri R, *et al.* Intracerebral hemorrhage associated with use of tadalafil (Cialis). *Neurology* 2008; 70: 1289–90.
2. Sheikh-Taha M, Alaywa RA. Subarachnoid hemorrhage associated with tadalafil. *Am J Health-Syst Pharm* 2011; 68: 1195–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tadalafil 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

As for Sildenafil, p. 2366.3.

Although phosphodiesterase type-5 inhibitors may be used cautiously with alpha blockers, UK licensed product information recommends against the use of tadalafil with doxazosin.

Antifungals. Priapism occurred in a man who took two separate doses of tadalafil 10 mg, at least one month apart, during *itraconazole* treatment.[1] He was able to take sildenafil during itraconazole treatment without adverse effect. See also Uses and Administration, p. 2368.2, for recommended tadalafil dosage when it is taken with inhibitors of the cytochrome P450 isoenzyme CYP3A4.

1. Galanti L, *et al.* Interaction between tadalafil and itraconazole. *Ann Pharmacother* 2005; 39: 200.

Antivirals. A study in healthy subjects given tadalafil with *ritonavir-boosted tipranavir* showed a significant increase in tadalafil concentrations initially, but once at steady state these HIV-protease inhibitors had little effect on tadalafil pharmacokinetics.[1] See also Uses and Administration, p. 2368.2, for recommended tadalafil dosage when it is taken with inhibitors of the cytochrome P450 isoenzyme CYP3A4.

1. Garraffo R, *et al.* Effect of tipranavir/ritonavir combination on the pharmacokinetics of tadalafil in healthy volunteers. *J Clin Pharmacol* 2011; 51: 1071–8.

Nitrates. Phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contra-indicated in patients receiving such drugs. An interaction between tadalafil and sublingual *glyceryl trinitrate* was reported to occur when glyceryl trinitrate was given within 24 hours after tadalafil but was no longer detectable at 48 hours.[1] Licensed product information recommends that if nitrate treatment is needed in a life-threatening situation then it should only be given at least 48 hours after the last dose of tadalafil and under close medical supervision.

1. Kloner RA, *et al.* Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol* 2003; 42: 1855–60.

Pharmacokinetics

Tadalafil is well absorbed after an oral dose. Peak plasma concentrations occur within 2 hours; the rate and extent of absorption are not affected by food.

Tadalafil is widely distributed into tissues and is about 94% bound to plasma proteins. It is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP3A4. The major metabolite, the methylcatechol glucuronide, is inactive. The mean half-life of tadalafil is about 17.5 hours.

Tadalafil is excreted, mainly as metabolites, in the faeces (61% of the dose), and to a lesser extent the urine (36% of the dose). Clearance may be reduced in the elderly and in patients with renal impairment.

References.

1. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; 45: 987–1003.
2. Porgue ST, *et al.* Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2006; 61: 280–8.
3. Porgue ST, *et al.* Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. *Br J Clin Pharmacol* 2007; 63: 24–35.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cialis; *Austral.*: Adcirca; Cialis; *Austria*: Adcirca; Cialis; *Belg.*: Adcirca; Cialis; *Braz.*: Adcirca; Cialis; *Canad.*: Adcirca; Cialis; *Chile*: Cialis; *China*: Cialis (希爱力); *Cz.*: Adcirca; Cialis; *Denm.*: Adcirca; Cialis; *Fin.*: Cialis; *Fr.*: Adcirca; Cialis; *Ger.*: Adcirca; Cialis; *Gr.*: Cialis; *Hong Kong*: Cialis; *Hung.*: Cialis; *India*: Erectalis; Forzest; Getgo; Manforce More; Oneaid; Tadacip; Zydalis; *Indon.*: Cialis; *Irl.*: Cialis; *Israel*: Cialis; *Ital.*: Cialis; *Malaysia*: Cialis; *Mex.*: Cialis; *Neth.*: Adcirca; Cialis; *Norw.*: Adcirca; Cialis; *NZ*: Cialis; *Philipp.*: Cialis; *Pol.*: Cialis; *Port.*: Adcirca; Cialis; *Rus.*: Cialis (Сиалис); *S.Afr.*: Cialis; *Singapore*: Cialis; *Spain*: Adcirca; Cialis; *Swed.*: Adcirca; Cialis; *Switz.*: Adcirca; Cialis; *Thai.*: Cialis; *Turk.*: Cialis; Lifta; Longis; Pasport; *UK*: Cialis; *Ukr.*: Cialis (Сиалис); *USA*: Adcirca; Cialis; *Venez.*: Cialis.

Pharmacopoeial Preparations
USP 36: Tadalafil Tablets.

Tamsulosin Hydrochloride

(BANM, USAN, rINNM)

Amsulosin Hydrochloride; Hidrocloruro de tamsulosina; LY-253351; Tamsulosiinihydrokloridi; Tamsulosin Hidroklorür; Tamsulosina, hidrocloruro de; Tamsulosine, Chlorhydrate de; Tamsulosinhydrochlorid; Tamsulosinhydroklorid; Tamsulosini Hydrochloridum; YM-617; YM-12617-1; Тамсулозина гидрохлорид; *R*-(-)-YM-12617.

(-)-(*R*)-5-[2-[[2-(o-Ethoxyphenoxy)ethyl]amino]-propyl]-2-methoxybenzenesulfonamide hydrochloride.

$C_{20}H_{28}N_2O_5S,HCl$=445.0

CAS — 106133-20-4 (tamsulosin); 106463-17-6 (tamsulosin hydrochloride).

ATC — G04CA02.

ATC Vet — QG04CA02.

UNII — 11SV1951MR.

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

Ph. Eur. 8: (Tamsulosin Hydrochloride). A white or almost white powder. Slightly soluble in water and in anhydrous alcohol; freely soluble in formic acid.

USP 36: (Tamsulosin Hydrochloride). A white or almost white crystalline powder. Slightly soluble in water and in dehydrated alcohol; sparingly soluble in methyl alcohol; practically insoluble in ether; freely soluble in formic acid. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Tamsulosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions similar to those of prazosin (p. 1474.1); it is reported to be more selective for the alpha$_{1A}$-adrenoceptor subtype, which accounts for about 70% of the α_1 adrenoceptors in the prostate. It is used in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction.

In benign prostatic hyperplasia, tamsulosin hydrochloride is given orally in a modified-release formulation, in a dose of 400 micrograms once daily. Licensed US product information states that the dose may be increased after 2 to 4 weeks, if necessary, to 800 micrograms once daily.

Reviews.

1. Wilde MI, McTavish D. Tamsulosin: a review of its pharmacological properties and therapeutic potential in the management of symptomatic benign prostatic hyperplasia. *Drugs* 1996; 52: 883–98.
2. Lee M. Tamsulosin for the treatment of benign prostatic hypertrophy. *Ann Pharmacother* 2000; 34: 188–99.
3. Lyseng-Williamson KA, *et al.* Tamsulosin: an update of its role in the management of lower urinary tract symptoms. *Drugs* 2002; 62: 135–67.
4. Ren R-M, *et al.* Efficacy and safety of tamsulosin for the treatment of benign prostatic hyperplasia: a meta analysis. *Chin Med J (Engl)* 2010; 123: 234–8.

Antidepressant-induced genito-urinary disorders. Tamsulosin was used successfully[1] to treat urinary hesitancy in 6 male patients receiving reboxetine. Painful ejaculation associated with reboxetine was also treated successfully[2] in 2 men.

1. Demyttenaere K, *et al.* Tamsulosin as an effective treatment for reboxetine-associated urinary hesitancy. *Int Clin Psychopharmacol* 2001; 16: 353–5.
2. Demyttenaere K, Huygens R. Painful ejaculation and urinary hesitancy in association with anddepressant therapy: relief with tamsulosin. *Eur Neuropsychopharmacol* 2002; 12: 337–41.

Prostatitis. Alpha$_1$-adrenoceptor blockers are one of a number of classes of drugs that have been tried for symptomatic relief in men with chronic prostatitis (p. 2350.2). In a 6-week multicentre, double-blind placebo-controlled study involving 58 men with moderate to severe chronic prostatitis/chronic pelvic pain syndrome, tamsulosin 400 micrograms daily produced greater symptomatic relief than placebo;[1] the effect was considered clinically significant for men with severe prostatitis. The benefit appeared to take several weeks to develop, and it was considered possible that longer exposure would produce additional benefit.

1. Nickel JC, *et al.* Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. *J Urol (Baltimore)* 2004; 171: 1594–7.

Renal calculi. In the conservative management of renal calculi (p. 2350.3) there is increasing interest in the possible use of drug treatment to ease the spontaneous passage of the stone down the ureter. Alpha$_1$-adrenoceptor blockers can decrease smooth muscle spasm in the ureter, reducing obstruction and improving urine flow. In studies[1-5] of patients with uncomplicated lower ureteral stones, tamsulosin has been reported to improve the rate of stone expulsion and expulsion time, and to reduce analgesic requirements. Tamsulosin was generally given orally in a dose of 400 micrograms daily for up to 4 weeks. Comparison groups were treated with various other antispasmodics including benzodiazepines, phloroglucinol, and nifedipine; in most studies patients were also treated with antibacterial prophylaxis, deflazacort, and NSAIDs. A review and meta-analysis[6] considered that tamsulosin was of benefit in aiding the expulsion of lower urinary tract stones less than 10 mm in diameter; the number needed to treat was 3.

A review[7] found evidence suggesting that adjunctive tamsulosin is safe and effective in enhancing the clearance of renal stones with a larger diameter when used with extracorporeal shock wave lithotripsy. Although evidence regarding ureteral stone clearance is inconclusive, adjunctive tamsulosin has been reported to reduce painful episodes.

1. Červenàkov I, *et al.* Speedy elimination of ureterolithiasis in lower part of ureters with the alpha 1-blocker–tamsulosin. *Int Urol Nephrol* 2002; 34: 25–9.
2. Dellabella M, *et al.* Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol (Baltimore)* 2003; 170: 2202–5.
3. Porpiglia F, *et al.* Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol (Baltimore)* 2004; 172: 568–71.
4. Yilmaz E, *et al.* The comparison and efficacy of 3 different α 1-adrenergic blockers for distal ureteral stones. *J Urol (Baltimore)* 2005; 173: 2010–12.
5. Dellabella M, *et al.* Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol (Baltimore)* 2005; 174: 167–72.
6. Arrabal-Martin M, *et al.* Treatment of ureteral lithiasis with tamsulosin: literature review and meta-analysis. *Urol Int* 2010; 84: 254–9.
7. Losek RL, Mauro LS. Efficacy of tamsulosin with extracorporeal shock wave lithotripsy for passage of renal and ureteral calculi. *Ann Pharmacother* 2008; 42: 692–6.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3 and p. 1475.1. Because tamsulosin is selective for α_1 receptors in the prostate the vasodilator effects may be less frequent. Tamsulosin may cause ejaculation abnormalities. Very rarely, Stevens-Johnson syndrome has been reported. Tamsulosin should be avoided in severe hepatic impairment.

Incidence of adverse effects. A study[1] using prescription event monitoring data for more than 12 000 patients treated with tamsulosin found that dizziness, headache, malaise, and hypotension were the adverse effects most commonly reported.

1. Mann RD, *et al.* The pharmacovigilance of tamsulosin: event data on 12 484 patients. *BJU Int* 2000; 85: 446–50.

Cataract surgery. In 2005 the manufacturers[1,2] of tamsulosin warned that a syndrome of flaccidity of the iris, progressive miosis, and potential prolapse (intraoperative floppy iris syndrome; IFIS) had been reported in some patients undergoing cataract surgery who were taking or had taken, alpha blockers. One group of workers[3] had reported that in one series of 741 patients undergoing cataract surgery, 15 of the 16 who developed IFIS had received tamsulosin. An earlier retrospective study of 511 similar patients by the same workers[3] had found IFIS in 10 of the 16 patients with a history of tamsulosin treatment but no cases in any of the other patients, including 11 patients given other alpha blockers. A retrospective case-controlled analysis found that patients taking tamsulosin within 14 days of cataract surgery were more than twice as likely to have serious postoperative ophthalmic events; no such association was found among those previously exposed to tamsulosin or with other alpha blockers used to treat benign prostatic hyperplasia.[4] The US manufacturer[2] stated that although most cases had occurred in patients who had been taking alpha blockers concurrently or up to 2 weeks before surgery the benefit of stopping such therapy before cataract surgery has not been established; a few cases had included patients who stopped alpha blockers up to 9 months before surgery. The manufacturers of tamsulosin recommend that patients being considered for cataract surgery should be questioned to ascertain whether they are taking the drug.[1,2] A literature review[5] found that other alpha blockers, including alfuzosin, doxazosin, and terazosin, have also been associated with IFIS in this patient group; however, IFIS has been most strongly associated with the use of tamsulosin. In the UK, the MHRA[6] has required the inclusion of a warning in the labelling of all alpha blockers advising patients to inform their cataract surgeon about past and current use of these drugs.

1. Boehringer Ingelheim (Canada). Important safety information on intraoperative floppy iris syndrome (IFIS) (issued 14th October 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/flomax_hpc-cps-eng.pdf (accessed 02/09/08)
2. Boodee HW [Boehringer Ingelheim Pharmaceuticals, Inc (USA)]. Important drug information for physicians (issued November 2005) Available at: http://www.fda.gov/medwatch/safety/2005/Flomax_dearhcp_nov22_PL.pdf (accessed 01/12/05)
3. Chang DF, Campbell JR. Intraoperative floppy iris syndrome associated with tamsulosin. *J Cataract Refract Surg* 2005; 31: 664–73.
4. Bell CM, *et al.* Association between tamsulosin and serious ophthalmic adverse events in older men following cataract surgery. *JAMA* 2009; 301: 1991–6.
5. Cantrell MA, *et al.* Intraoperative floppy iris syndrome associated with α$_1$-adrenergic receptor antagonists. *Ann Pharmacother* 2008; 42: 558–63.
6. MHRA/CHM. α -1 adrenoceptor antagonists: intraoperative floppy iris syndrome. *Drug Safety Update* 2007;1 (1): 4–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON2031802 (accessed 17/06/08)

Interactions

As for Prazosin Hydrochloride, p. 1475.1.

Tamsulosin is metabolised by cytochrome P450 isoenzymes CYP2D6 and CYP3A4, and inhibitors of these isoenzymes may increase exposure to tamsulosin. It should be used with caution, if at all, with strong inhibitors of CYP3A4 and such combinations should be avoided in patients who are CYP2D6 poor metabolisers. Caution is also required when giving tamsulosin with a moderate inhibitor of CYP3A4, with strong or moderate inhibitors of CYP2D6, or in CYP2D6 poor metabolisers, particularly at oral tamsulosin doses higher than 400 micrograms daily.

Caution is also advised when tamsulosin is given with warfarin or diclofenac as the elimination of tamsulosin may be increased and therefore the exposure reduced. Furosemide may also reduce exposure, but tamsulosin concentrations remain within the normal range.

Pharmacokinetics

Tamsulosin is absorbed from the gastrointestinal tract and is almost completely bioavailable. The extent and rate of absorption are reduced by food. After oral doses of an immediate-release preparation, peak plasma concentrations occur after about 1 hour. Tamsulosin is about 99% bound to plasma proteins. It is metabolised slowly in the liver primarily by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4; it is excreted mainly in the urine as metabolites and some unchanged drug. The plasma elimination half-life has been reported to be between 4 and 5.5 hours.

Some of the pharmacokinetic values cited above may be altered when tamsulosin is given as a modified-release preparation, the form in which it is usually used; for instance, peak plasma concentrations occur about 6 hours after a dose and the apparent elimination half-life may be 10 to 15 hours.

Renal impairment. Plasma-tamsulosin concentrations were reported to be increased in patients with renal impairment when compared with subjects with normal renal function.[1,2] However, plasma concentrations of unbound, pharmacologically active drug were similar in both groups and it was suggested that the raised total plasma concentrations were due to an increase in plasma protein binding.

1. Koiso K, *et al.* Pharmacokinetics of tamsulosin hydrochloride in patients with renal impairment: effects of α_1-acid glycoprotein. *J Clin Pharmacol* 1996; 36: 1029–38.
2. Woltz M, *et al.* Pharmacokinetics of tamsulosin in subjects with normal and varying degrees of impaired renal function: an open-label single-dose and multiple-dose study. *Eur J Clin Pharmacol* 1998; 54: 367–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aclosan; Biprokam; Controlpros; Espontal; Lostam; Omnic; Prostoklar; Reduprost; Secotex; Talosin; Tamsuna; Tansiloprost; Uralos; Uroprost-Q; *Austral.*: Flomax†; Flomaxtra; *Austria*: Aglandin; Alna; Tamsu; Tamsunova†; *Belg.*: Omic; Ranomax; *Braz.*: Contiflo; Omnic Secotex; Tamsulon; *Canad.*: Flomax; *Chile*: Eupen; Gotely; Omnic; Prostall; Secotex; Sulix; Vi-Uril; *China*: BenTe (本特); Bi Tan (必坦); Harnal (哈乐); Jida BenTe (积大本特); Qi Suo (齐索); *Cz.*: Apo-Tamis; Damurgin; Fokusin; Lannatam; Omnic; Solesmin; Taflosin; Tamipro; Tamsec†; Tamsuda; Tamsulonorm; Tamurox; Tanyz; Urostad; Urotam; *Denm.*: Cepalux; Masulin; Omnic; Omnistad; Prostacure; Ranomax; Tamsin; Tamsukon†; Tamsulogen†; Tamsunorm; *Fin.*: Expros; Omnic; Promictan; Tamictor; Tamsact; Tamsin; Tamsu-Anlini; TamsuCinfa; Tamsu-Garan; Tamsulogen; Tamsumin; TamsuPli; *Fr.*: Josir; Mecir; Omexel; Omix; *Ger.*: Alna; Omnic; Prostacure; Prostadil; Prostazid†; Tadin; Tamsu-Q†; Tamsublock; Tamsulo-Isis†; Tamsumedin†; Tamsunar; *Gr.*: Miktosan; Novelio; Omnic; Pradif; Prosolvin; Ranomax; Sintamel; Tamsol; Tamsolet; Tamsulijn; Zidrolin; *Hong Kong*: Harnal; *Hung.*: Flosin; Fokusin; Omipro; Omnic; Provosal; Ranomax; Tamsol; Tamsudil; Tamsugen; Tamsulonorm; Tanyz; Totalprost; Uro-Tam; Urostad; *India*: Alfatam; Contiflo; Dynapres; Gotam; Urimax; *Indon.*: Harnal; *Irl.*: Kirnom; Omnexel; Omnic; Omsil; Prolosin; Tacap; Tamnexyl; Tamnic; Tamsu; Tamsulas†; *Israel*: Omnic; Promnix; Tamsulin; *Ital.*: Antunes; Botam; Lura; Omnic; Pradif; Probena; Tamlic; *Jpn*: Harnal; *Malaysia*: Harnal; *Mex.*: Amzuvag; Asoflon; Fedpros; Hipebe; Jumslim; Secadryckel; Secotex; Suprosina; *Neth.*: Mapelor; Omnic; Protam; Sebrane; Talpro; Taluso; Tamagsyn; Tamsin; Tamsuda; Tamsulijn; *Norw.*: Cepalux; Omnic; *NZ*: Flomax; Flomaxtra; *Philipp.*: Harnal; Pimax; Prozelax; *Pol.*: Apo-Tamis; Bazetham; Fokusin; Omipro; Omnic; Omsal; Prostamnic; Proximic; Ranlosin; Symlosin; Tamsec; Tamsudil; Tamsugen; TamsuLek; Tanyz; Uprox; Urostad; *Port.*: Omnic; Pradif; Sulin; Tacap; *Rus.*: Fokusin (Фокусин); Hyperprost (Гиперпрост); Omnic (Омник); Omsulosin (Омсулозин); Revokarin (Ревокарин); Sonizin (Сонизин); Tamsulon (Тамсулона); Tanyz (Таниз-К); Tulosin (Тулозин); *S.Afr.*: Beniprosin; Flomax; Prostaflo; Tamsul; Uromax; *Singapore*: Harnal; *Spain*: Inreq; Manfredol†; Omnic; Sebrane; Urolosin; Vetevel†; Zuantrip; *Switz.*: Omix; Pradif; Tamsunax; *Thai.*: Harnal; *Turk.*: Flomax; Floprost; Tamidra; Tamprost; Tocas; Uromax; *UK*: Bazetham†; Contiflo; Cositam; Diffundox; Flomax; Flomaxtra; Galebon; Stronazon; Tabphyn; Tamfrex; *Ukr.*: Adenorm (Аденорм); Flosin (Флосин); Fokusin (Фокусин); Omix (Омікс); Omnic (Омник); Omnimax (Омнимакс); Ranoprost (Рапопрост); Tamsol (Тамсол); Tamsonic (Тамсоник)†; Tamsulid (Тамсулид); Urofrin (Урофрин); *USA*: Flomax; *Venez.*: Secotex; Tamsulon.

Multi-ingredient Preparations. *Austral.*: Duodart; *Belg.*: Combodart; *Canad.*: Jalyn; *Cz.*: Duodart; *Denm.*: Combodart; *Fin.*: Duodart; *Ger.*: Duodart; *Gr.*: Duodart; *Hung.*: Duamild; *India*: Contiflo-OD-P; Dutas-T; Finabald-T; Finast T; Flokind-P; Gerflo; Urimax F; *Irl.*: Combodart; *Israel*: Duodart; *Neth.*: Combodart; *Norw.*: Duodart; *Pol.*: Duodart; *Port.*: Combodart; *Spain*: Duodart; *Switz.*: Duodart; *UK*: Combodart; *USA*: Jalyn.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Tamsulosin Capsules; Prolonged-release Tamsulosin Tablets;
USP 36: Tamsulosin Hydrochloride Capsules.

Tolterodine Tartrate *(BANM, USAN, rINNM)*

Kabi-2234 (tolterodine); PNU-200583E; Tartrato de tolterodina; Tolterodin Tartrat; Tolterodina, tartrato de; Tolterodine L-Tartrate; Toltérodine, Tartrate de; Tolterodini Tartras; Тольтеродина Тартрат.

(+)-(*R*)-2-{α-[2-(Diisopropylamino)ethyl]benzyl}-*p*-cresol tartrate.

$C_{22}H_{31}NO,C_4H_6O_6$=475.6

CAS — 124937-51-5 (tolterodine); 124937-52-6 (tolterodine tartrate).

ATC — G04BD07.

ATC Vet — QG04BD07.

UNII — 5T619TQR3R.

Uses and Administration

Tolterodine tartrate is a tertiary antimuscarinic with actions similar to those of atropine (p. 1310.3); it is claimed to have a greater selectivity for the muscarinic receptors of the bladder. Tolterodine is used in the management of urinary frequency, urgency, and incontinence in detrusor instability. Usual oral doses of tolterodine tartrate are 2 mg twice daily; modified-release preparations are given in a usual dose of 4 mg once daily. Doses of 1 mg twice daily (or 2 mg daily as a modified-release preparation) are recommended in patients experiencing troublesome adverse effects. Licensed US product information advises that the dose of tolterodine should not exceed 2 mg daily in patients receiving potent CYP3A4 inhibitors; UK product information recommends against such combinations. See below for doses in patients with hepatic or renal impairment and for doses in children.

Administration in children. Although tolterodine is not licensed in the UK for use in children, the *BNFC* suggests that an oral dose of 1 mg daily, increased according to response to a maximum of 2 mg twice daily, may be used in children from 2 years of age for urinary frequency, urgency, and incontinence. A similar dose is given to children aged 5 years and above for the treatment of nocturnal enuresis; one dose should be given at bedtime. Children stabilised on 2 mg twice daily of a conventional formulation may be transferred to 4 mg once daily of a modified-release preparation.

Administration in hepatic or renal impairment. Oral doses of 1 mg of tolterodine tartrate twice daily (or 2 mg daily as a modified-release preparation) are recommended by UK and US licensed product information in patients with hepatic or severe renal impairment.

Benign prostatic hyperplasia. Although there have been concerns about the use of antimuscarinics in patients with symptomatic benign prostatic hyperplasia (p. 2347.1) some patients have lower urinary tract symptoms suggestive of overactive bladder, and antimuscarinics such as tolterodine are increasingly being used to treat such symptoms, either alone or as adjuncts.

References.

1. Kaplan SA, *et al.* Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. *J Urol (Baltimore)* 2005; 174: 2273–5.
2. Kaplan SA, *et al.* Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 2006; 296: 2319–28. Correction. *ibid.*; 297: 1195. Correction. *ibid.*; 298: 1864.
3. Roynet ES, *et al.* Effect of tolterodine extended release with or without tamsulosin on measures of urgency and patient reported outcomes in men with lower urinary tract symptoms. *J Urol (Baltimore)* 2008; 180: 1034–41.

Nocturnal enuresis. Tolterodine has been tried with desmopressin for nocturnal enuresis (p. 2349.1) in children with an incomplete response to desmopressin.[1] A 66% reduction in the risk of bed-wetting episodes was reported with tolterodine and desmopressin treatment compared with desmopressin alone.

1. Austin PF, *et al.* Combination therapy with desmopressin and an anticholinergic medication for nonresponders to desmopressin for monosymptomatic nocturnal enuresis: a randomized, double-blind, placebo-controlled trial. *Pediatrics* 2008; 122: 1027–32.

Urinary incontinence. Tolterodine is used as an alternative to oxybutynin in the treatment of urge incontinence (see p. 2349.2). Tolterodine is said to have fewer adverse effects than oxybutynin, but the *BNF* states that its efficacy and adverse effects are comparable to modified-release oxybutynin.

References.

1. Harvey M-A, *et al.* Tolterodine versus oxybutynin in the treatment of urge urinary incontinence: a meta-analysis. *Am J Obstet Gynecol* 2001; 185: 56–61.
2. Jacquetin B, Wyndaele J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. *Eur J Obstet Gynecol Reprod Biol* 2001; 98: 97–102.
3. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). *Curr Med Res Opin* 2002; 18: 177–84.
4. Swift S, *et al.* A new once-daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. *Int Urogynecol J Pelvic Floor Dysfunct* 2003; 14: 50–4.
5. Diokno AC, *et al.* Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc* 2003; 78: 687–95.
6. Khullar V, *et al.* Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. *Urology* 2004; 64: 269–74.
7. Sand PK, *et al.* A comparison of extended-release oxybutynin and tolterodine for treatment of overactive bladder in women. *Int Urogynecol J Pelvic Floor Dysfunct* 2004; 15: 243–8.
8. Nijman RJ, *et al.* Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. *J Urol (Baltimore)* 2005; 173: 1334–9.
9. Rovner ES. Tolterodine for the treatment of overactive bladder: a review. *Expert Opin Pharmacother* 2005; 6: 653–66.
10. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)
11. Jumadilova Z, *et al.* Retrospective evaluation of outcomes in patients with overactive bladder receiving tolterodine versus oxybutynin. *Am J Health-Syst Pharm* 2006; 63: 2357–64.
12. Salvatore S, *et al.* Tolterodine for the treatment of overactive bladder. *Expert Opin Pharmacother* 2008; 9: 1249–55.
13. Ulahannan D, Wagg A. The safety and efficacy of tolterodine extended release in the treatment of overactive bladder in the elderly. *Clin Interv Aging* 2009; 4: 191–6.
14. Chung DE, Te AE. Tolterodine extended-release for overactive bladder. *Expert Opin Pharmacother* 2009; 10: 2181–94.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. For a report of adverse ocular effects of tolterodine, see Effects on the Eyes under Oxybutynin, p. 2362.1. Tolterodine should be used with caution in patients with hepatic or renal impairment. *Animal* studies have shown that high doses may cause fetal toxicity and it is recommended that tolterodine should be avoided during pregnancy.

Prolongation of the QT interval has occurred in controlled studies using both therapeutic and higher doses of tolterodine, and although changes from baseline did not cross the threshold of concern, the clinical implications are unclear. Licensed product information therefore warns that tolterodine should be used with caution in patients with QT prolongation or relevant risk factors, such as electrolyte disturbances, bradycardia, pre-existing cardiac disease, or the concomitant use of other drugs known to prolong the QT interval. Patients with raised tolterodine concentrations because of drug interactions (see below) would also be at increased risk, particularly poor metabolisers (see Pharmacokinetics, p. 2371.1).

References.

1. Layton D, *et al.* Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring. *Drug Safety* 2001; 24: 703–13.
2. Garely AD, Burrows L. Benefit-risk assessment of tolterodine in the treatment of overactive bladder in adults. *Drug Safety* 2004; 27: 1043–57.
3. Malhotra BK, *et al.* Thorough QT study with recommended and supratherapeutic doses of tolterodine. *Clin Pharmacol Ther* 2007; 81: 377–85.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tolterodine 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

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

There is a risk of interactions between tolterodine and drugs that inhibit cytochrome P450 isoenzymes CYP2D6 (but see Antidepressants, below), or CYP3A4. For comment on dosage of tolterodine with potent CYP3A4 inhibitors (such as the macrolide antibacterials erythromycin or clarithromycin, or the azole antifungals ketoconazole, itraconazole, or miconazole), see Uses and Administration, above. Tolterodine can prolong the QT interval and should be used with caution in patients receiving other drugs known to have this effect, particularly class Ia and class III antiarrhythmics.

Anticholinesterases. For mention of an interaction between tolterodine and *donepezil* or *rivastigmine*, see Antimuscarinics, under Donepezil, p. 391.2.

Anticoagulants. For reference to the effect of tolterodine on the activity of *warfarin*, see under Antimuscarinics, p. 1532.2.

Antidepressants. The SSRI *fluoxetine* is a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6 and use with tolterodine has resulted in more than a fourfold increase

in the area under the serum concentration-time curve (AUC) of tolterodine, associated with an approximate 20% decrease in the AUC of its 5-hydroxymethyl metabolite.[1] However, since both are active these changes were thought likely to result in little clinical difference, and licensed product information does not recommend a dose adjustment when tolterodine is given with fluoxetine.

1. Brynne N, *et al.* Fluoxetine inhibits the metabolism of tolterodine—pharmacokinetic implications and proposed clinical relevance. *Br J Clin Pharmacol* 1999; 48: 553–63.

Gastrointestinal drugs. In a study[1] in healthy subjects, a dose of *antacid* was found to speed up the release of tolterodine from a modified-release preparation, probably as a result of the increase in gastric pH. Plasma-tolterodine concentrations were increased, but the half-life and area under the plasma concentration-time curve were not significantly affected. *Omeprazole* was reported to have a similar effect in another study.[2] The possible clinical effect of this change in drug release is unclear.

1. Sathyan G, *et al.* Effect of antacid on the pharmacokinetics of extended-release formulations of tolterodine and oxybutynin. *Clin Pharmacokinet* 2004; 43: 1059–68.
2. Dmochowski R, *et al.* Effect of the proton pump inhibitor omeprazole on the pharmacokinetics of extended-release formulations of oxybutynin and tolterodine. *J Clin Pharmacol* 2005; 45: 961–8.

Pharmacokinetics

Peak plasma concentrations of tolterodine occur 1 to 3 hours after an oral dose. It is highly bound to plasma proteins. Tolterodine is mainly metabolised in the liver by the cytochrome P450 isoenzyme CYP2D6 to the active 5-hydroxymethyl derivative (DD-01); in a minority of poor metabolisers tolterodine is metabolised by CYP3A4 isoenzymes to its inactive *N*-dealkylated derivative. The absolute bioavailability of tolterodine is normally about 17%, and the half-life is 2 to 3 hours; these increase in poor metabolisers to an absolute bioavailability of 65% and a half-life of about 10 hours. However, the clinical use of tolterodine is not affected by these differences in metabolism because the exposure to unbound tolterodine in poor metabolisers is similar to the combined exposure to unbound tolterodine and the active 5-hydroxymethyl metabolite in extensive metabolisers. Tolterodine is excreted primarily in the urine with about 17% appearing in the faeces; less than 1% of a dose is excreted as unchanged drug.

References.

1. Brynne N, *et al.* Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. *Int J Clin Pharmacol Ther* 1997; 35: 287–95.
2. Brynne N, *et al.* Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine. *Clin Pharmacol Ther* 1998; 63: 529–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Breminal; Coli-Q; Detrusitol; Toltem; Urginol; *Austral.*: Detrusitol; *Austria*: Detrusitol; *Belg.*: Detrusitol; *Braz.*: Detrusitol; *Canad.*: Detrol; *Chile*: Detrusitol; Eltoven; *China*: BeiKe (贝可); Bu Mai Ding (布迈定); Detrusitol (得妥); Le Zai (乐在); NeiQing (内青); Ning Tong (宁通); SheNiTing (舍尼亭); Te Su An (特苏安); *Cz.*: Detrusitol; Uroflow; *Denm.*: Detrusitol; *Fin.*: Detrusitol; *Fr.*: Detrusitol; *Ger.*: Detrusitol; *Gr.*: Detrusitol; *Hong Kong*: Detrusitol; *Hung.*: Detrusitol; *India*: Detrusitol; Dezrolala; Flochek; Terol; *Indon.*: Detrusitol; *Irl.*: Detrusitol; *Israel*: Detrusitol; *Ital.*: Detrusitol; *Malaysia*: Detrusitol; *Mex.*: Detrusitol; Hipolter; *Neth.*: Detrusitol; Tolespes; Tulerin; Uroline; *Norw.*: Detrusitol; *NZ*: Detrusitol; *Pol.*: Defur; Detrusitol; Uroflow; *Port.*: Detrusitol; *Rus.*: Detrusitol (Детрузитол); Roliten (Ролитен); Urotol (Уротол); *S. Afr.*: Detrusitol; *Singapore*: Detrusitol; *Spain*: Detrusitol; Urotrol; *Swed.*: Detrusitol; *Switz.*: Detrusitol; *Thai.*: Detrusitol; *Turk.*: Detrusitol; Toldin; Toltex; *UK*: Blerone; Detrusitol; Inconex; Mariosea; Neditol; Preblacon; Santizor; *Ukr.*: Detrusitol (Детрузитол); Roliten (Ролитен); Urotol (Уротол); *USA*: Detrol; *Venez.*: Detrusitol.

Trospium Chloride *(BAN, USAN, rINN)*

Cloruro de trospio; IP-631; Trospii Chloridum; Trospio cloridas; Trospio, cloruro de; Trospium, Chlorure de; Trospiumchlorid; Trospium-chlorid; Trospiumklorid; Trospiumkloridi; Trospiyum Klorür; Троспия Хлорид.

3α-Benziloyloxynortropane-8-spiro-1′-pyrrolidinium chloride.

$C_{25}H_{30}ClNO_3$=428.0

CAS — 10405-02-4.

ATC — G04BD09.

ATC Vet — QG04BD09.

UNII — 1E6682427E.

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

Ph. Eur. 8: (Trospium Chloride). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

USP 36: (Trospium Chloride). A colourless or white to slightly yellow crystalline powder. Very soluble in water; freely soluble in methyl alcohol. pH of a 1% solution in carbon dioxide-free water is 5.0 to 7.0. Protect from light.

Uses and Administration

Trospium chloride is a quaternary ammonium antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used for the management of urinary frequency, urgency, and incontinence in detrusor instability or detrusor hyperreflexia. It has also been used as an antispasmodic.

The immediate-release preparation is given orally in usual doses of 20 mg twice daily before meals on an empty stomach. Lower doses of 20 mg once daily may be warranted in patients aged 75 years and over. The need for continued treatment should be assessed at regular intervals of 3 to 6 months. A modified-release preparation is also available in some countries; the usual oral dose is 60 mg once daily in the morning, at least one hour before food. For use in patients with hepatic or renal impairment, see below.

Trospium chloride has also been given by slow intravenous injection. An inhaled formulation of trospium chloride for the treatment of chronic obstructive pulmonary disease is also being developed.

References.

1. Walter F, *et al.* Bioavailability of trospium chloride after intravesical instillation in patients with neurogenic lower urinary tract dysfunction: a pilot study. *Neurourol Urodyn* 1999; 18: 447–53.
2. Frohlich G, *et al.* Trospium chloride in patients with detrusor overactivity: meta-analysis of placebo-controlled, randomized, double-blind, multi-center clinical trials on the efficacy and safety of 20 mg trospium chloride twice daily. *Int J Clin Pharmacol Ther* 2002; 40: 295–303.
3. Halaska M, *et al.* Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol* 2003; 20: 392–9.
4. Lopez Pereira P, *et al.* Trospium chloride for the treatment of detrusor instability in children. *J Urol (Baltimore)* 2003; 170: 1978–81.
5. Zinner N, *et al.* Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol (Baltimore)* 2004; 171: 2311–15.
6. Rovner ES. Trospium chloride in the management of overactive bladder. *Drugs* 2004; 64: 2433–46.
7. Singh-Franco D, *et al.* Trospium chloride for the treatment of overactive bladder with urge incontinence. *Clin Ther* 2005; 27: 511–30.
8. Rudy D, *et al.* Multicenter phase III trial studying trospium chloride in patients with overactive bladder. *Urology* 2006; 67: 275–80.
9. Menarini M, *et al.* TcP128-Study Group. Trospium chloride in patients with neurogenic detrusor overactivity: is dose titration of benefit to the patients? *Int J Clin Pharmacol Ther* 2006; 44: 623–32.
10. Staskin D, *et al.* Trospium Study Group. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. *J Urol (Baltimore)* 2007; 178: 978–83.
11. Biastre K, Burnakis T. Trospium chloride treatment of overactive bladder. *Ann Pharmacother* 2009; 43: 283–95.

Administration in hepatic impairment. Licensed product information for trospium chloride states that maximum plasma concentrations and area under the concentration-time curve were increased in patients with mild (Child-Pugh score 5 to 6) or moderate (Child-Pugh score 7 to 12) hepatic impairment compared with healthy subjects. There is no information regarding the use of trospium chloride in patients with severe hepatic impairment.

UK licensed product information advises caution in those with mild to moderate impairment, and advises against treatment in severe hepatic impairment. US licensed product information for both the immediate-release and the modified-release preparations advises caution in those with moderate to severe hepatic impairment. No specific dosage recommendations are given in either the UK or US product information.

Administration in renal impairment. Trospium chloride is mainly eliminated through active tubular secretion. Licensed product information states that increases in maximum plasma concentrations, area under the concentration-time curve, and half-life have been seen in patients with severe renal impairment given the immediate-release preparation; the pharmacokinetics of trospium chloride have not been studied in those with mild or moderate renal impairment.

UK licensed product information for the immediate-release preparation advises caution in those with mild to moderate renal impairment, while allowing for an oral dose of trospium chloride 20 mg once daily, or every alternate day, in those with severe renal impairment, defined as creatinine clearance (CC) of between 10 and 30 mL/minute per 1.73 m^2.

US licensed product information for the immediate-release preparation recommends a dose of 20 mg daily at bedtime for those with severe renal impairment (defined as CC less than 30 mL/minute). The modified-release preparation is not recommended for use in patients with severe renal impairment.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Trospium should be used with caution in patients with hepatic or renal impairment. *Animal* studies have shown that trospium crosses the placenta and is distributed into breast milk; licensed product information therefore recommends that caution should be observed during pregnancy and breast feeding.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

After oral doses of trospium chloride, peak plasma concentrations occur in 4 to 6 hours. The bioavailability of trospium chloride is reduced by the simultaneous intake of food, especially with a high fat content. Plasma protein binding ranges from about 50% to about 80%. Trospium is excreted in the urine mainly by active renal tubular secretion as unchanged drug; about 10% appears as the spiroalcohol metabolite. The plasma half-life has been reported to be between 10 and 20 hours for the immediate-release preparation, and about 35 hours for the modified-release preparation. The mean half-life has been reported to be prolonged twofold in patients with severe renal impairment (creatinine clearance between 8 and 32 mL/minute). Trospium has been reported to cross the placenta and has been detected in the milk of *rats*.

Reviews.

1. Doroshyenko O, *et al.* Clinical pharmacokinetics of trospium chloride. *Clin Pharmacokinet* 2005; 44: 701–20.

For a study of the bioavailability of trospium chloride after intravesical instillation, see References, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Spasmex; *Austria*: Inkontan; Rekont Spasmolyt; Uraplex; Urivesc; *Canad.*: Sanctura; Trosec; *Chile*: Spasmex; *China*: Spasmo-Lyt (顺腔利); *Cz.*: Spasmed; Spasmex†; Uraplex; *Denm.*: Ceris; Spasmo-Lyt; Spasmoplex†; Uraplex; Urivesc; *Fin.*: Spasmo-Lyt; *Fr.*: Ceris; *Ger.*: Spasmex; Spasmo-Rhoival TC†; Spasmo-Urgenin TC; Spasmolyt; Trospi; Urivesc; *Gr.*: Uraplex; Urivesc; *Irl.*: Ceris; Flotros; Regurin; *Israel*: Spasmex; Spasmo-Lyt; *Ital.*: Uraplex†; Urivesc; *Malaysia*: Spasmolyt; *Port.*: Spasmoplex; Urivesc; *Rus.*: Spasmex (Спазмекс); *S.Afr.*: Uricon; *Singapore*: Spasmolyt; *Spain*: Uraplex; Urivesc; *Switz.*: Spasmo-Urgenine Neo; *Thai.*: Spasium; Spasmex; Spasmo-Lyt; Urivesc; *Turk.*: Spasmex; *UK*: Flotros; Regurin; *Ukr.*: Spasmo-Lyt (Спазмо); *USA*: Sanctura.

Multi-ingredient Preparations. *Austria*: Spasmo-Urgenin; *Spain*: Spasmo-Urgenin; *Thai.*: Spasmo-Urgenin.

Pharmacopoeial Preparations

USP 36: Trospium Chloride Tablets.

Udenafil *(USAN, rINN)*

DA-8159; Udénafil; Udenafilo; Udenafilum; Уденафил.

3-(1-Methyl-7-oxo-3-propyl-4,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-*N*-[2-[(2*RS*)-1-methylpyrrolidin-2-yl]ethyl]-4-propoxybenzenesulfonamide.

$C_{25}H_{36}N_6O_4S$=516.7.

CAS — 268203-93-6.

UNII — L5IB4XLY36.

Profile

Udenafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2). It is used in the management of erectile dysfunction in an oral dose of 100 or 200 mg, 30 minutes to 2 hours before sexual intercourse. It should not be taken more than once in 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Malaysia*: Zydena; *Philipp.*: Zydena; *Rus.*: Zydena (Зидена).

Vardenafil *(rINN)*

Vardénafil; Vardenafilum; Варденафил.

1-[[3-(3,4-Dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*]-*as*-triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethylpiperazine.

$C_{23}H_{32}N_6O_4S$=488.6

CAS — 224785-90-4.

ATC — G04BE09.

ATC Vet — QG04BE09.

UNII — UCE6F4125H.

Vardenafil Dihydrochloride *(USAN, rINNM)*

Dihidrocloruro de vardenafil; Vardénafil, Dichlorhydrate de; Vardenafili Dihydrochloridum; Варденафила Дигидрохлорид.

$C_{23}H_{32}N_6O_4S.2HCl$=561.5

CAS — 224789-15-5.

ATC — G04BE09.

ATC Vet — QG04BE09.

UNII — 5O8R96XMH7.

Vardenafil Hydrochloride *(USAN, rINNM)*

Bay-38-9456; Hidrocloruro de vardenafil; Vardénafil, Chlorhydrate de; Vardenafil Monohydrochloride; Vardenafili Hydrochloridum; Варденафила Гидрохлорид.

$C_{23}H_{32}N_6O_4S.HCl$=525.1

CAS — 224785-91-5.

ATC — G04BE09.

ATC Vet — QG04BE09.

UNII — 5M8S2CU0TS.

Uses and Administration

Vardenafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2). It is used in the management of erectile dysfunction (p. 2348.2). Vardenafil is given orally as the hydrochloride trihydrate although doses are expressed in terms of the base; vardenafil hydrochloride trihydrate 11.85 mg is equivalent to about 10 mg of vardenafil.

The usual dose of the *conventional oral formulation* is 10 mg taken about 25 minutes to one hour before sexual intercourse. The dose may be increased or decreased depending on response. The maximum recommended dose is 20 mg, and vardenafil should not be taken more than once in 24 hours. The dose may be taken with or without food, but onset of activity may be delayed if taken with a high-fat meal.

- An initial dose of 5 mg is recommended in elderly patients, which may be increased up to the maximum of 20 mg if necessary.
- In patients stabilised on alpha blocker therapy, the initial dose of vardenafil should be no more than 5 mg daily and it should not be taken within 6 hours of the alpha blocker, although this interval may not be necessary with alfuzosin or tamsulosin.
- A maximum daily dose of vardenafil 5 mg is advised in patients taking erythromycin (dose not specified in licensed product information), itraconazole (200 mg daily), or ketoconazole (200 mg daily). A daily dose of 2.5 mg is recommended for those taking clarithromycin (dose not specified in licensed product information), itraconazole (400 mg daily), or ketoconazole (400 mg daily).
- A maximum dose of vardenafil 2.5 mg every 24 hours is recommended in patients taking HIV-protease inhibitors. This dose should be reduced to 2.5 mg every 72 hours in those taking ritonavir-boosted regimens, although this combination may be best avoided (see also Interactions, below).

An *orodispersible formulation* that disintegrates on the tongue before swallowing is also available; the usual and maximum dose is 10 mg taken 25 minutes to one hour before sexual intercourse. The bioavailability of vardenafil after dosing with this formulation is greater than that with the conventional form and, consequently, the two forms are not bioequivalent.

For doses in hepatic or renal impairment, see below.

Reviews.

1. Keating GM, Scott LJ. Vardenafil: a review of its use in erectile dysfunction. *Drugs* 2003; 63: 2673–2703.
2. Crowe SM, Streetman DS. Vardenafil treatment for erectile dysfunction. *Ann Pharmacother* 2004; 38: 77–85.
3. Markou S, *et al.* Vardenafil (Levitra) for erectile dysfunction: a systematic review and meta-analysis of clinical trial reports. *Int J Impot Res* 2004; 16: 470–8.
4. van Ahlen H, *et al.* The real-life safety and efficacy of vardenafil: an international post-marketing surveillance study—results from 29 358 German patients. *J Int Med Res* 2005; 33: 337–48.
5. Reffelmann T, Kloner RA. Vardenafil: a selective inhibitor of phosphodiesterase-5 for the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2007; 8: 965–74.
6. Eardley I, *et al.* Global experiences with vardenafil in men with erectile dysfunction and underlying conditions. *Int J Clin Pract* 2008; 62: 1594–1603.
7. Morales AM, *et al.* Vardenafil for the treatment of erectile dysfunction: an overview of the clinical evidence. *Clin Interv Aging* 2009; 4: 463–72.
8. Sanford M. Vardenafil orodispersible tablet. *Drugs* 2012; 72: 87–98.

Administration in hepatic impairment. When given as the *conventional oral formulation*, an initial dose of 5 mg of vardenafil is recommended by UK licensed product information in patients with mild to moderate hepatic impairment (Child-Pugh category A to B), which may be increased if necessary, according to response and tolerability. The maximum dose recommended in patients with moderate hepatic impairment is 10 mg. Vardenafil has not been evaluated in severe hepatic impairment (Child-Pugh category C).

The *orodispersible formulation* should not be used in patients with moderate or severe hepatic impairment. It may be given, in a dose of 10 mg, to those with mild impairment who can tolerate a 5-mg dose of the conventional formulation.

Administration in renal impairment. No dose adjustment of vardenafil is needed in patients with mild to moderate renal impairment. An initial dose of 5 mg of the *conventional oral formulation* is recommended by UK licensed product information in patients with a creatinine clearance of less than 30 mL/minute; this may be increased to 10 mg and then to 20 mg if necessary, according to response and tolerability. US licensing information does not consider adjustment to be necessary. The *orodispersible formulation*, in a dose of 10 mg, may be given to those patients who can tolerate a 5-mg dose of the conventional formulation.

The pharmacokinetics of vardenafil have not been studied in patients requiring dialysis.

Adverse Effects and Precautions

As for Sildenafil, p. 2365.2 and p. 2366.2. Photosensitivity has also been reported. Vardenafil may prolong the QT interval and is best avoided in patients with relevant risk factors such as hypokalaemia, congenital QT prolongation, or the use of antiarrhythmics of class Ia or class III. Dosage reductions may be required in patients with hepatic or renal impairment.

Effects on the cardiovascular system. References.

1. Thadani U, *et al.* The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. *J Am Coll Cardiol* 2002; 40: 2006–12.

Interactions

As for Sildenafil, p. 2366.3. The use of vardenafil with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 (such as HIV-protease inhibitors, some azole antifungals, and macrolide antibacterials) is generally best avoided; if thought to be essential, dosage of vardenafil must be reduced and suggested doses are given above. Use with ketoconazole and itraconazole is contra-indicated in men older than 75 years of age. An enhanced hypotensive effect may be seen if vardenafil is taken with nifedipine. Vardenafil may prolong the QT interval and its use with antiarrhythmics of class Ia or class III should be avoided.

Pharmacokinetics

Vardenafil is rapidly absorbed after an oral dose, with a bioavailability of about 15%. Peak plasma concentrations are attained within 30 to 120 minutes; the rate of absorption is reduced when vardenafil is given with a high-fat meal.

Vardenafil is widely distributed into tissues and is about 95% bound to plasma proteins. It is metabolised in the liver primarily by cytochrome P450 isoenzymes CYP3A4 (the major route) as well as CYP3A5 and CYP2C isoforms. The major metabolite produced by desethylation of vardenafil also has some activity. The terminal half-life is about 4 to 5 hours.

Vardenafil is excreted as metabolites mainly in the faeces (91 to 95%), and to a lesser extent in the urine (2 to 6%). Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

References.

1. Rajagopalan P, *et al.* Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. *J Clin Pharmacol* 2003; 43: 260–7.
2. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; 45: 987–1003.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Levitra; ***Austral.***: Levitra; ***Austria***: Levitra; Vivanza; ***Belg.***: Levitra; ***Braz.***: Levitra; Vivanza†; ***Canad.***: Levitra; ***Chile***: Levitra; ***China***: Levitra (艾力达); ***Cz.***: Levitra; Vivanza; ***Denm.***: Levitra; ***Fin.***: Levitra; ***Fr.***: Levitra; ***Ger.***: Levitra; ***Gr.***: Levitra; Vivanza; ***Hong Kong***: Levitra; ***Hung.***: Levitra; ***Indon.***: Levitra; ***Irl.***: Levitra; Vivanza; ***Israel***: Levitra; ***Ital.***: Levitra; ***Malaysia***: Levitra; ***Mex.***: Levitra; ***Neth.***: Levitra; Vivanza; ***Norw.***: Levitra; ***NZ***: Levitra; ***Philipp.***: Levitra; ***Pol.***: Levitra; Vivanza; ***Port.***: Levitra; Vivanza; ***Rus.***: Levitra (Левитра); ***S.Afr.***: Levitra; ***Singapore***: Levitra; ***Spain***: Levitra; Vivanza; ***Swed.***: Levitra; ***Switz.***: Levitra; Vivanza; ***Thai.***: Levitra; ***Turk.***: Levitra; ***UK***: Levitra; ***Ukr.***: Levitra (Левитра); ***USA***: Levitra; Staxyn; ***Venez.***: Levitra.

Yohimbine Hydrochloride *(BAN)*

Aphrodine Hydrochloride; Chlorhydrate de Québrachine; Corynine Hydrochloride; Hidrocloruro de Afrodina; Yohimbina, hidrocloruro de; Yohimbine, chlorhydrate de; Yohimbinhydrochlorid; Yohimbini hydrochloridum; Йохимбина Гидрохлорид.

Methyl 17α-hydroxy-yohimban-16α-carboxylate hydrochloride.

$C_{21}H_{26}N_2O_3.HCl$=390.9

CAS — 146-48-5 (yohimbine); 65-19-0 (yohimbine hydrochloride).

ATC — G04BE04.

ATC Vet — QG04BE04; QV03AB93.

UNII — NB2E1YP49F.

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

Ph. Eur. 8: (Yohimbine Hydrochloride). A white or slightly yellowish, crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 3.5 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Yohimbine Hydrochloride). A white to yellow powder. Slightly soluble in water and in alcohol; soluble in boiling water. Store in airtight containers.

Profile

Yohimbine is the principal alkaloid of the bark of the yohimbe tree, *Pausinystalia yohimbe* (*Corynanthe yohimbi*) (Rubiaceae); it is also found in *Rauwolfia serpentina*. It is an alpha$_2$-adrenoceptor blocker with a short duration of action. It has an antidiuretic effect and produces increases in heart rate and blood pressure. It has been reported to cause CNS effects including anxiety and manic reactions. It has been given orally in the treatment of erectile dysfunction (p. 2348.2) and for its alleged aphrodisiac properties but convincing evidence of such an effect is lacking. It is contra-indicated in renal or hepatic disease.

Adverse effects. A warning about the potential adverse effects, including anxiety, manic reactions, bronchospasm, and a lupus-like syndrome, associated with yohimbine taken in health food products.[1] Interactions with tricyclic antidepressants and with phenothiazines might also occur. Acute severe neurotoxicity has been reported.[2]

1. De Smet PAGM, Smeets OSNM. Potential risks of health food products containing yohimbe extracts. *BMJ* 1994; 309: 958.
2. Giampreti A, *et al.* Acute neurotoxicity after yohimbine ingestion by a body builder. *Clin Toxicol* 2009; 47: 827–9.

Uses. References to the use of yohimbine in erectile dysfunction.

1. Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomised clinical trials. *J Urol (Baltimore)* 1998; 159: 433–6.
2. Tam SW, *et al.* Yohimbine: a clinical review. *Pharmacol Ther* 2001; 91: 215–43.
3. Lebret T, *et al.* Efficacy and safety of a novel combination of L-arginine glutamate and yohimbine hydrochloride: a new oral therapy for erectile dysfunction. *Eur Urol* 2002; 41: 608–13.
4. Guay AT, *et al.* Yohimbine treatment of organic erectile dysfunction in a dose-escalation trial. *Int J Impot Res* 2002; 14: 25–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Yocon; ***Belg.***: Yocoral; ***Braz.***: Yomax; ***Canad.***: Yocon†; ***Chile***: Yocon; ***Denm.***: Virigen†; ***Fr.***: Yocoral; ***Ger.***: Yocon; ***Port.***: Zumba; ***UK***: Prowess Plain; ***Ukr.***: Yochimbin Spiegel (Йохімбін Шпігель)†; ***USA***: Aphrodyne; Yocon.

Multi-ingredient Preparations. ***Arg.***: Ferona†; Optimina Plus; ***Braz.***: Libiplus; Tonaton; ***Hong Kong***: Sessoforte†; Wari-Procomil†; ***Indon.***: Sirec; ***UK***: Prowess; ***Ukr.***: Yohimbex-Garmonia (Йохимбекс-Гармония).

Homoeopathic Preparations. ***Fr.***: Kalium Phosphoricum Complexe No 100; ***Rus.***: Damiana-Plus (Дамиана-Плюс).

Pharmacopoeial Preparations

USP 36: Yohimbine Injection.

Vaccines Immunoglobulins and Antisera

The agents described in this section are immunological agents used for both active and passive immunisation.

Active immunisation is the exposure of the immune system to antigens in the form of micro-organisms or products of their activity in order to stimulate production of antibodies and acquired cell-mediated responses with a specific protective capacity. It may be a natural process after infection, or an artificial process induced by giving *vaccines*. It is inevitably a slow process dependent upon the rate at which the antibodies can be produced. Although the terms vaccination and immunisation are often used synonymously and interchangeably, *vaccination* simply refers to giving a vaccine whereas *immunisation* implies the development of protective levels of antibodies.

Passive immunisation, which results in immediate short-term protection, may be achieved by giving exogenous antibodies in the form of *antisera* (of animal origin) or *immunoglobulins*.

Antisera

Antisérums; Antisueros; Immunsera; Sueros inmunológicos; Антисыворотки.

Description

Antisera (immunosera) are sterile preparations containing immunoglobulins obtained from the serum of immunised animals by purification. The term antisera includes antitoxins, which are antibodies that combine with and neutralise specific toxins, and antivenins (antivenoms), which are antitoxins directed against the toxic principle of the venoms of poisonous animals such as certain snakes and arthropods.

Antisera are obtained from healthy animals immunised by injections of the appropriate toxins or toxoids, venins, or suspensions of micro-organisms or other antigens. The specific immunoglobulins may be obtained from the serum by fractional precipitation and enzyme treatment or by other chemical or physical means. A suitable antimicrobial preservative may be added, and is invariably added if the product is issued in multidose containers. The Ph. Eur. 8 directs that when antisera contain phenol, the concentration is not more than 0.25%. The antiserum is distributed aseptically into sterile containers, which are sealed so as to exclude micro-organisms. Alternatively they may be supplied as freeze-dried preparations for reconstitution immediately before use.

Uses and Administration

Antisera have the specific power of neutralising venoms or bacterial toxins, or combining with the bacterium, virus, or other antigen used for their preparation. Most antisera in current use are antitoxins or antivenins. The use of antisera to induce passive immunity has declined; immunoglobulins are preferred. Although antisera are defined as being of animal origin (see above), the term antisera has been used in some countries to describe antitoxins of human origin (immunoglobulins).

Adverse Effects and Precautions

Reactions are liable to occur after the injection of any serum of animal origin. Anaphylaxis (type I hypersensitivity reaction, p. 610.1) may occur, with hypotension, dyspnoea, urticaria, and shock, which requires management as a medical emergency (see Anaphylaxis and Anaphylactic Shock, p. 1293.2).

Serum sickness (type III hypersensitivity reaction, p. 610.1) may also occur, frequently 7 to 10 days after the injection of serum of animal origin.

Before injecting serum, information should be obtained whenever possible as to whether the patient is subject to hypersensitivity disorders or has received serum injections before. Sensitivity testing should be performed before giving antisera. The patient must be kept under observation after giving a full dose of antisera. Adrenaline injection and resuscitation facilities should be available.

Immunoglobulins

Immunglobuline; Inmunoglobulinas; Иммуноглобулины.

Description

Immunoglobulins are produced by B lymphocytes as part of the humoral response to foreign antigens. Immunoglobulins used in clinical practice are preparations containing antibodies, usually prepared from human plasma or serum, and mainly comprise IgG. Normal immunoglobulin, prepared from material from blood donors, contains several antibodies against infectious diseases prevalent in the general population, whereas specific immunoglobulins contain minimum specified levels of one antibody. Antibodies may also be prepared by genetic engineering techniques.

Uses and Administration

Immunoglobulins are used for passive immunisation, thus conferring immediate protection against some infectious diseases. They are preferred to antisera of animal origin as the incidence of adverse reactions is lower.

It is generally important to follow the conferment of passive immunity, which is largely an emergency procedure, by the injection of suitable antigens to produce active immunity.

Adverse Effects

Local reactions with pain and tenderness at the site of intramuscular injection may follow the use of immunoglobulins. Hypersensitivity reactions, including, rarely, anaphylactic reactions, have also been reported; such reactions, though, are far less frequent than after the use of antisera of animal origin.

Some immunoglobulins are available as intravenous preparations. Systemic reactions with fever, chills, facial flushing, headache, and nausea may occur, particularly at high rates of infusion.

Precautions

Strenuous efforts are made to screen human donor material used in the preparation of immunoglobulins; the transmission of infections, including hepatitis B and HIV, which has been associated with the use of certain blood products (see p. 1135.3), does not appear to be a problem with the immunoglobulins currently in use.

IgA, present in some immunoglobulin preparations, may give rise to the production of anti-IgA antibodies in patients with IgA deficiencies, with the consequent risk of anaphylactic reactions. For precautions in such patients, see Hypersensitivity under Adverse Effects and Precautions in Normal Immunoglobulins, p. 2407.3.

Interactions

Immunoglobulins may interfere with the ability of live vaccines to induce an immune response and a suitable interval should separate their use (see Vaccines, Interactions, p. 2375.3).

Vaccines

Vacunas; Вакцины.

Description

Vaccines are traditionally preparations of antigenic materials that are given with the objective of inducing in the recipient active immunity to specific infecting agents or toxins or antigens produced by them. They may contain living or killed micro-organisms, bacterial toxoids, or antigenic material from particular parts of the infecting organism, which may be derived from the organism or produced by recombinant DNA technology. Vaccines may be single-component vaccines or mixed combined vaccines. Vaccines against some non-infectious diseases are being developed.

Storage. All vaccines are sensitive to heat to differing extents, with oral poliomyelitis vaccines and measles vaccines the most heat-sensitive of the commonly used vaccines. Freeze-dried vaccines become much more heat-sensitive once reconstituted. The effect of heat on vaccines is generally irreversible loss of potency, but in some cases heat exposure may also cause the vaccine to become more reactogenic. The system used for storing and distributing vaccines at sufficiently low temperature is called the cold chain, and consists of a series of storage and transport links all designed to keep the vaccine at the correct temperature until it reaches the user. WHO recommends[1] that oral poliomyelitis vaccines be stored at -25 to -15 degrees and that, in general, freeze-dried vaccines should be stored at 2 to 8 degrees.

Some vaccines are also sensitive to freezing, notably hepatitis B vaccines and Haemophilus influenzae vaccines, and care should be taken not to store them at too low a temperature.[1]

In addition to temperature sensitivity, some vaccines are also sensitive to light, such as BCG vaccines, measles-containing vaccines, and rubella-containing vaccines. These are sometimes supplied in darker glass vials for protection, but care should be taken to protect them from sunlight and ultraviolet light, including fluorescent lights.[2]

Further advice concerning vaccine storage is given in the references below.[3-6] Preliminary study has suggested[7] that it may be possible to develop vaccines that are stable without refrigeration by drying the antigens in a suspension of sucrose and trehalose.

1. WHO. *Temperature sensitivity of vaccines.* Geneva: WHO, 2006. Also available at: http://www.who.int/vaccines-documents/DocsPDF06/847.pdf (accessed 23/04/10)
2. WHO. *Cold chain, vaccines and safe-injection equipment management.* Geneva: WHO, 2008. Also available at: http://www.who.int/immunization_delivery/systems_policy/MLM_module1.pdf (accessed 23/04/10)
3. Department of Vaccines and Other Biologicals. *Temperature monitors for vaccines and the cold chain.* Geneva: WHO, 1999. Also available at: http://www.who.int/vaccines-documents/DocsPDF/www9804.pdf (accessed 15/09/05)
4. CDC. Notice to readers: guidelines for maintaining and managing the vaccine cold chain. *MMWR* 2003; 52: 1023–5. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5242.pdf (accessed 24/05/06)
5. Australian Government Department of Health and Ageing. National vaccine storage guidelines: strive for 5 (2005). Available at: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/DF94731AD8CBF34ECA2575BD001C8129/$File/strive-4-five.pdf (accessed 27/08/10)
6. Public Health Agency of Canada. National vaccine storage and handling guidelines for immunization providers (2007). Available at: http://www.phac-aspc.gc.ca/publicat/2007/nvshgip-idemv/pdf/nvshgip-idemv-eng.pdf (accessed 27/08/10)
7. Alcock R, *et al.* Long-term thermostabilization of live poxviral and adenoviral vaccine vectors at supraphysiological temperatures in carbohydrate glass. *Sci Transl Med* 2010; 2: 19ra12.

Uses and Administration

Vaccines are used for active immunisation as a prophylactic measure against some infectious diseases. They provide partial or complete protection for months or years. For inactivated vaccines, a slight and rather slow antibody response of primarily immunoglobulin M (IgM) (the primary response) is produced after the first or second dose but, when a further dose is given after a suitable interval, a prompt antibody response follows and high concentrations of IgG occur in the blood (the secondary response). Though the antibody concentration may later fall, a further dose of vaccine promptly restores it. For most live vaccines only one dose is required, although 3 doses of live (oral) poliomyelitis vaccines are needed to achieve complete immunisation. Some inactivated vaccines contain an adjuvant such as aluminium hydroxide or aluminium phosphate to enhance the immune response.

Protection against several infectious diseases may be provided in early life by active immunisation and national schedules for **childhood** immunisation are regularly reviewed and updated. Schedules for routine immunisation of infants and children are generally designed to fit in with routine health checks and landmark events such as school starting and leaving ages. National immunisation schedules should be consulted for full details of local recommendations.

In the UK, the following schedule of vaccination and immunisation is recommended:

- at 2 months of age, the first dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine (p. 2385.3), plus a first dose of pneumococcal conjugate vaccine (p. 2410.1) and a first dose of a rotavirus vaccine (p. 2416.1)
- at 3 months of age, a second dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine, plus the first dose of meningococcal C conjugate vaccine (p. 2401.3) and a second dose of a rotavirus vaccine
- at 4 months of age, a third dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine, plus a second dose of pneumococcal conjugate vaccine
- at about 12 to 13 months of age, a third dose of pneumococcal conjugate vaccine, plus a first dose of measles, mumps, and rubella vaccine (p. 2400.2), plus a booster dose of a combined *Haemophilus influenzae* and meningococcal C conjugate vaccine (p. 2388.1)

The symbol † denotes a preparation no longer actively marketed

- at 3 years 4 months to 5 years, a reinforcing dose of a combined diphtheria, tetanus, pertussis (acellular component), and poliomyelitis (inactivated) vaccine (p. 2385.2) and a second dose of measles, mumps, and rubella vaccine
- at 12 to 13 years of age, 3 separate doses of human papillomavirus vaccine (p. 2392.2) for all girls
- at around 14 years, a booster dose of a low-dose diphtheria, tetanus, and poliomyelitis (inactivated) vaccine (p. 2386.2) and a meningococcal C conjugate vaccine

The following schedule is usually recommended in the **USA:**

- at birth, the first dose of hepatitis B vaccine (p. 2389.3)
- at age 1 to 2 months, a second dose of hepatitis B vaccine
- at 2 months, a first dose of diphtheria, tetanus, and pertussis (acellular component) vaccine (p. 2383.3), plus a *Haemophilus influenzae* vaccine (p. 2387.2), a pneumococcal conjugate vaccine (p. 2410.1), a poliomyelitis (inactivated) vaccine (p. 2411.1) and a rotavirus vaccine (p. 2416.1)
- at 2 to 18 months, a course of a meningococcal vaccine (p. 2401.3) with or without a *Haemophilus influenzae* vaccine to high-risk children
- at 4 months, a second dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, plus the second doses of a *Haemophilus influenzae* vaccine, pneumococcal conjugate vaccine, poliomyelitis (inactivated) vaccine, and rotavirus vaccine
- at 6 months, the third dose of *Haemophilus influenzae* vaccine if necessary (depending on the type of vaccine used), a third dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, a third dose of pneumococcal conjugate vaccine, and a third dose of rotavirus vaccine if necessary (depending on the type of vaccine used)
- at 6 to 18 months, the third doses of hepatitis B and poliomyelitis (inactivated) vaccines
- from 6 months to 18 years, annual influenza vaccine
- from 12 to 23 months, 2 doses (6 to 18 months apart) of a hepatitis A vaccine (p. 2388.3)
- at 12 to 15 months, a reinforcing dose of *Haemophilus influenzae* vaccine, the first dose of measles, mumps, and rubella vaccine, the first dose of varicella-zoster vaccine (p. 2423.3) and the fourth dose of pneumococcal conjugate vaccine
- at 15 to 18 months, the fourth dose of diphtheria, tetanus, and pertussis (acellular component) vaccine
- at 2 to 18 years, pneumococcal polysaccharide vaccine (as an addition to previous dosage with pneumococcal conjugate vaccine) in certain high-risk groups
- at 2 to 10 years, meningococcal C conjugate vaccine (2 doses, 2 months apart) to children with terminal complement deficiencies or asplenia and other high-risk groups; meningococcal polysaccharide vaccine may alternatively be used
- at 4 to 6 years, the fifth dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, the fourth dose of poliomyelitis (inactivated) vaccine, the second dose of measles, mumps, and rubella vaccine, and the second dose of varicella-zoster vaccine
- at age 11 to 12 years, a sixth dose of low-dose diphtheria, tetanus, and pertussis (acellular component) plus a first dose of quadrivalent meningococcal C conjugate vaccine in those not previously vaccinated (meningococcal polysaccharide vaccine may alternatively be used); the first dose of human papillomavirus vaccine (p. 2392.2) may be given to girls, the second dose is given 2 months after the first dose and the third dose is given 6 months after the first dose
- at 16 years, a booster dose of meningococcal C conjugate vaccine (meningococcal polysaccharide vaccine may alternatively be used)

Immunisation schedules for older children and **adults** are also produced, along with recommendations for vaccination of high-risk groups, including the immunocompromised and the elderly, and of travellers.

In addition to vaccines directed against bacteria and viruses, advances are being made in producing vaccines against fungi, protozoa, and helminths, and for non-infective diseases including cancer (see p. 757.3) and auto-immune disorders.

Development of novel vaccine formulations and delivery methods is continuing, including transdermal and transmucosal systems. Genetic manipulation of foodstuffs is being investigated with the aim of producing edible vaccines.

Immunisation schedules. References to routine immunisation schedules in the UK[1] and USA.[2-4]

1. DoH. *Immunisation Against Infectious Disease* 2006 (updated 14th March, 2013): "The Green Book". Available at: https://www.gov.uk/government/publications/green-book-the-complete-current-edition (accessed 18/04/13)
2. CDC. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for persons aged 0 through 18 years– United States, 2013. *MMWR Surveill Summ* 2013; 62 (suppl 1): 2–8. Correction. *ibid.*: 256. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/su6201a2.htm (accessed 21/03/13)
3. CDC. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for adults aged 19 Years and older– United States, 2013. *MMWR Surveill Summ* 2013; 62 (suppl 1): 9–19. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/su6201a3.htm (accessed 21/03/13)
4. Committee on Infectious Diseases. Recommended childhood and adolescent immunization schedule—United States, 2013. *Pediatrics* 2013; 131: 397–8. Also available at: http://pediatrics.aappublications.org/content/131/2/397.full.pdf+html (accessed 22/05/13)

EXPANDED PROGRAMME ON IMMUNIZATION. In 1974 the World Health Assembly adopted a resolution creating the Expanded Programme on Immunization (EPI), the aim of which was to provide immunisation against 6 target diseases (diphtheria, measles, pertussis, poliomyelitis, tetanus, and tuberculosis) for all children throughout the world by 1990. Hepatitis B, pneumococcal, and *Haemophilus influenzae* infections were later added to the list of target diseases and more recently rotavirus, and, for girls, human papillomavirus vaccines were also added. Although the attention of WHO had been focussed mainly on the developing countries, it was emphasised that the programme was not created exclusively for these countries. Besides WHO, many other organisations, including UNICEF, are involved. Since 2000 much work has been carried out under the auspices of the Global Alliance for Vaccination and Immunisation (GAVI) and in 2006 UNICEF and WHO established the Global Immunization Vision and Strategy (GIVS) to raise global immunisation coverage for these common preventable diseases to at least 90% in every country over 5 years, and then to sustain coverage.

Although many cases of the target diseases and many deaths have been prevented, vaccine coverage, especially for measles and neonatal tetanus is still low. It is particularly important to immunise children as early in life as possible and not to withhold vaccines from those with minor illness or malnutrition. Vaccine uptake was around 70% in 1990 compared with less than 5% in 1974. By 2003, all 192 member states of WHO were routinely immunising against diphtheria, measles, pertussis, poliomyelitis, and tetanus before the age of 18 months. Also, 158 member states were routinely immunising against tuberculosis, but routine BCG vaccination has been stopped in some countries, including the UK, due to low risk and prevalence of disease.

A schedule designed to provide protection for all children at the earliest possible age broadly recommends:

- at birth, a dose of BCG vaccine (p. 2378.1). A monovalent hepatitis B vaccine (p. 2389.3) should be given as soon as possible after birth; further doses (which may be given as a combined vaccine) are then given at 6, 10 (optional), and 14 weeks. A dose of the poliomyelitis (OPV) vaccine (p. 2411.1) can be given at birth in endemic or recently endemic countries
- at 6 weeks, the first dose of a diphtheria, tetanus, and pertussis vaccine (p. 2383.3), plus a *Haemophilus influenzae* vaccine (p. 2387.2), a pneumococcal conjugate vaccine (p. 2410.1), a rotavirus vaccine (p. 2416.1), and a poliomyelitis vaccine (OPV)
- at 10 weeks, a second dose of diphtheria, tetanus, and pertussis vaccine, plus the second doses of a *Haemophilus influenzae* vaccine, a pneumococcal conjugate vaccine, a rotavirus vaccine, and a second (or third) dose of a poliomyelitis vaccine (OPV)
- at 14 weeks, the third dose of diphtheria, tetanus, and pertussis vaccine, plus the third doses of *Haemophilus influenzae* vaccine, a pneumococcal conjugate vaccine, rotavirus vaccine (only for those completing a course of *RotaTeq*), and a third (or fourth) dose of a poliomyelitis vaccine (OPV)
- at 9 to 12 months, the first dose of a measles vaccine (p. 2398.3) with a dose of rubella vaccine (p. 2417.1); a second dose of a measles vaccine should be given 4 weeks after the first dose
- at 1 to 6 years, the fourth (booster) dose of diphtheria, tetanus, and pertussis vaccine
- at age 9 to 13 years, the first dose of human papillomavirus (quadrivalent) vaccine (p. 2392.2) may be given to girls, the second dose is given 2 months after the first dose and the third dose is given 6 months after the first dose. *Alternatively*, at age 10 to 13 years, the first dose of human papillomavirus (bivalent) vaccine may be given to girls, the second dose is given 1 month after the first dose and the third dose is given 6 months after the first dose

Inactivated polio vaccine (IPV) alone may be given as an alternative to OPV alone (or an IPV/OPV sequential schedule) in countries that have the lowest risk of both wild-strain polio viruses importation and transmission. A primary series of 3 doses should be started at 2 months of age and the next doses given at 4 to 8 week intervals. If the primary series starts earlier (e.g. at 6 weeks of age) then a booster dose should be given after an interval of 6 months or more.

In addition to these vaccines children living in certain areas may also be given Japanese encephalitis vaccine (p. 2396.2), tick-borne encephalitis vaccine (p. 2422.1), and/or yellow fever vaccine (p. 2424.3). Immunisation schedules for children in some high-risk populations, older children, and adults are also provided.

References.

1. WHO. WHO vaccine-preventable diseases: monitoring system 2010 global summary. Geneva: WHO, 2010. Also available at: http://whqlibdoc.who.int/hq/2010/WHO_IVB_2010_eng.pdf (accessed 10/04/13)
2. WHO. WHO recommendations for routine immunization–summary tables (issued 15 November, 2012). Available at: http://www.who.int/immunization/policy/immunization_tables/en/index.html (accessed 26/03/13)

Immunisation of immunocompromised patients. Immunocompromised patients may require immunisation against opportunistic infections but immune response to vaccination may be impaired (see Precautions, p. 2375.2), and there is a risk of disseminated infection with live vaccines.

Recommendations for immunisation of HIV-positive individuals have varied, particularly with regard to live vaccines.

It is generally recommended that vaccines used for routine immunisation in childhood may be given to asymptomatic HIV-positive persons, providing they are not immunosuppressed, but that BCG and yellow fever vaccines should not be given at all.[1,2] WHO recommends[3] that an extra dose of measles vaccine may be given at 6 months of age with the standard dose given as soon after 9 months of age as possible.

Some detailed guidance on vaccination of immunocompromised children is provided by the Royal College of Paediatrics and Child Health in the UK[4] and by the Children's HIV Association of UK and Ireland.[5] Guidance on immunisation of HIV-infected adults is provided by the British HIV Association.[6]

1. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isfIGX (accessed 27/08/10)
2. Eley B. Immunization in patients with HIV infection: are practical recommendations possible? *Drugs* 2008; 68: 1473–81.
3. WHO. Measles vaccines: WHO position paper. *Wkly Epidem Rec* 2009; 84: 349–60. Also available at: http://www.who.int/wer/2009/wer8435.pdf (accessed 16/12/09)
4. Royal College of Paediatrics and Child Health. Immunisation of the immunocompromised child: best practice statement February 2002. Available at: http://www.rcpch.ac.uk/doc.aspx?id_Resource=1768 (accessed 15/07/08)
5. Riordan A. Children's HIV Association of UK and Ireland. Immunisation of HIV-infected children, June 2007 [under review]. Available at: http://www.chiva.org.uk/health/guidelines/immunisation (accessed 27/08/10)
6. Gerrett AM, *et al.* British HIV Association Immunisation Subcommittee. Immunisation guidelines for HIV-infected adults 2008. Available at: http://www.bhiva.org/documents/Guidelines/Immunisation/Immunisation2008.pdf (accessed 10/02/10)

Immunisation for travellers. A guide entitled *International Travel and Health* is published annually by WHO.[1] In 2010 the following information regarding certification of vaccination was given.

A *yellow fever* vaccination certificate is now the only one that may be mandated by international regulations, although some countries require other vaccinations before entry is permitted. The vaccine used must be approved by WHO and given at a designated centre. Vaccination is strongly recommended for travel outside the urban areas of countries in the yellow fever endemic zone even if these countries have not officially reported the disease and do not require evidence of vaccination on entry. Many countries require a certificate from travellers arriving from infected areas or from countries with infected areas, or who have been in transit through those areas. Some countries require a certificate from all entering travellers including those in transit; although there is no epidemiological justification for this requirement, and it is clearly in excess of the International Health Regulations (WHO recommendations for prevention of the international spread of diseases), travellers may find that it is strictly enforced, particularly for persons going to Asia from Africa or South America. The validity period of international certificates of vaccination against yellow fever is 10 years, beginning 10 days after vaccination.

Some polio-free countries require evidence of *polio* vaccination before travellers from endemic countries are permitted entry; Saudi Arabia also requires pilgrims to be vaccinated against *meningococcal* disease.

No country or territory any longer requires a certificate of *cholera* immunisation as the introduction of cholera into any country cannot be prevented by cholera vaccination.

Now that *smallpox* has been eradicated, smallpox vaccination is no longer required by any country.

Apart from vaccinations required by countries for entry to their territory, other vaccinations are either recommended by WHO for general protection against certain

diseases or advised in certain circumstances. A vaccination plan should be established, taking into account the traveller's destination, overall state of health and current immune status, the duration and type of travel, and the time available before travel.

Further information for international travellers is also often provided by national authorities including those in the UK[2] and USA.[3]

1. WHO. *International Travel and Health*. Geneva: WHO, 2010. Also available at: http://www.who.int/ith/en/ (accessed 02/07/10)
2. The National Travel Health Network and Centre. *Health Information for Overseas Travel*. Available at: http://www.nathnac.org/pro/yellowbook_revision.htm (accessed 16/11/9)
3. CDC. *The Yellow Book*:2010. Available at: http://wwwn.cdc.gov/travel/content/yellowbook/home-2010.aspx (accessed 16/11/09)

Infection eradication. Eradication of infectious diseases has proved more difficult than was hoped, and smallpox is the only disease to have been recognised officially as having been eradicated so far. Eradication is defined as the extinction of the pathogen that causes the infectious disease in question, whereas in elimination the disease disappears but the causative agent remains. Of the target diseases of WHO's Expanded Programme on Immunization (see p. 2374.2), many of the factors necessary for elimination are present for each of the diseases, but some are not. *Measles* is so highly communicable a disease that a vaccine efficacy rate of about 95% is probably not high enough even to eliminate, much less eradicate, the disease. However, immunisation campaigns have produced substantial reductions of infection rate in some countries, although repeated vaccination may be necessary. *Pertussis* is also highly infectious and the vaccine is almost certainly not effective enough. *Tetanus* is not eradicable as the causative organism is ubiquitous. However, elimination of neonatal tetanus may be possible although it depends on protection of more than 80% of infants at birth. This depends not only on maternal vaccination but also on delivery practices. For *poliomyelitis*, countries that are efficient at giving vaccines have proved remarkably successful not only in practically eliminating the disease but also in virtually eradicating the organism. *Tuberculosis* is clearly not eradicable at present and *diphtheria* has many features that suggest it cannot be easily eradicated. Prospects for eradicating *congenital rubella syndrome* are more encouraging and the prospects for elimination or eradication of *mumps* are probably similar to those of rubella.

Other factors that may contribute to the failure of vaccination policies in eradicating disease include: concern, often unfounded, over the safety of vaccines and the perpetuation of invalid contra-indications, the use of inappropriate indicators for the efficacy of vaccines, the suitability of different types of vaccine and of vaccination schedules, difficulties in vaccine supply, and social and behavioural pressures which reduce compliance with vaccination schedules.

Vaccine development. The WHO Initiative for Vaccine Research (IVR) supports and facilitates the development, clinical evaluation, and worldwide access to safe, effective, and affordable vaccines against infectious diseases of public health importance, especially in developing countries. The Global Vaccine Research Forum hosts an annual conference to discuss vaccine research and development issues, and to update research agendas. Information is frequently updated by WHO.[1,2]

1. WHO. State of the art of new vaccines: research and development (revised 2005). Available at: http://www.who.int/vaccine_research/documents/stateoftheart/en/index.html (accessed 29/04/06)
2. WHO. New vaccines against infectious diseases: research and development status (April 2005, updated February 2006). Available at: http://www.who.int/vaccine_research/documents/en/Status_Table.pdf (accessed 29/04/06)

Adverse Effects

Injection of a vaccine may be followed by a local reaction, possibly with inflammation and lymphangitis. An induration or sterile abscess may develop at the injection site. Fever, headache, and malaise may start a few hours after injection and last for 1 or 2 days. Hypersensitivity reactions may occur and anaphylaxis has been reported rarely.

Further details, if appropriate, of adverse effects of vaccines may be found in the respective individual monographs.

Anaphylaxis. In a retrospective study[1] in the USA conducted to quantify the risk of anaphylaxis after vaccination of children and adolescents, only 5 cases potentially associated with vaccines were identified from more than 7.5 million doses given. Vaccines implicated were generally given in combination and included the following components: diphtheria and tetanus; diphtheria, tetanus, and pertussis; hepatitis B; Haemophilus influenzae; measles, mumps, and rubella; and oral poliomyelitis. One case followed measles, mumps, and rubella vaccine given alone. It was concluded that vaccine-associated anaphylaxis is a rare event.

Recommendations[2] have been issued in the USA for the evaluation and management of patients with suspected allergy to vaccines.

1. Bohlke K, *et al.* Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; 112: 815–20.
2. Kelso JM, *et al.* Joint Task Force on Practice Parameters for Allergy & Immunology. Adverse reactions to vaccines. *Ann Allergy Asthma Immunol* 2009; 103 (suppl 2): S1–S14.

Long-term effects. The introduction of routine childhood vaccination has been accompanied by concerns over the safety and possible long term sequelae of some commonly used vaccines. Difficulties have arisen in distinguishing temporal and causal associations and in some cases the perceived dangers of vaccination have impeded uptake. Among the disorders that have been temporally (but generally not causally) associated with childhood vaccination are neurological disorders, sudden infant death syndrome, type 1 diabetes mellitus, and demyelinating disorders. Information on adverse effects associated with specific vaccines can be found under diphtheria, tetanus, and pertussis vaccines (p. 2384.1), hepatitis B vaccines (p. 2390.3), influenza vaccines (p. 2394.3), measles, mumps, and rubella vaccines (p. 2400.2), and pertussis vaccines (p. 2409.1).

Additives or excipients have sometimes been alleged to be the cause of adverse reactions—see below for further details.

References.

1. Jefferson T. Vaccination and its adverse effects: real or perceived. *BMJ* 1998; 317: 159–60.
2. Ball LK, *et al.* Risky business: challenges in vaccine risk communication. *Pediatrics* 1998; 101: 453–8.
3. Hiltunen M, *et al.* Immunisation and type 1 diabetes mellitus: is there a link? *Drug Safety* 1999; 20: 207–12.
4. Institute for Vaccine Safety Diabetes Workshop Panel. Childhood immunizations and type 1 diabetes: summary of an Institute for Vaccine Safety workshop. *Pediatr Infect Dis J* 1999; 18: 217–22.
5. Stratton K, *et al.* *Immunization safety review: multiple immunizations and immune dysfunction*. Washington DC: National Academy Press, 2002. Also available at: http://www.nap.edu/catalog.php?record_id=10306 (accessed 14/07/08)
6. Offit PA, Hackett CJ. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics* 2003; 111: 653–9.
7. Wraith DC, *et al.* Vaccination and autoimmune disease: what is the evidence? *Lancet* 2003; 362: 1659–66.
8. Stratton K, *et al.* *Immunization safety review: vaccinations and sudden unexpected death in infancy*. Washington DC: National Academy Press, 2003. Also available at: http://www.nap.edu/catalog.php?record_id=10649 (accessed 14/07/08)
9. CDC. Surveillance for safety after immunization: vaccine adverse event reporting system (VAERS) — United States, 1991–2001. *MMWR* 2003; 52 (SS-1): 1–24. Correction. *ibid.*: 113.
10. Hvild A, *et al.* Childhood vaccination and type 1 diabetes. *N Engl J Med* 2004; 350: 1398–1404.
11. Koppen S, *et al.* No epidemiological evidence for infant vaccination to cause allergic disease. *Vaccine* 2004; 22: 3375–85.
12. Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. *Vaccine* 2005; 23: 3876–86.

Effects of adjuvants. *Aluminium hydroxide* has been used frequently as an adsorbent in vaccines. A review[1] found significantly more erythema and induration with aluminium-containing vaccines than with plain ones. There was, however, no evidence of serious or long-lasting adverse effects that could be attributed to aluminium salts.

Thiomersal has been used as a preservative but because of alleged adverse effects is no longer used as widely as it once was (see Vaccines, under Thiomersal, p. 1772.2 for further details). However, the comment has been made that in developing countries far more benefit will be seen from protecting children with current, inexpensive, domestically-manufactured thiomersal-containing vaccines, than by investing in thiomersal-free alternatives.[2]

1. Jefferson T, *et al.* Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. *Lancet Infect Dis* 2004;4: 84–90.
2. 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.

Effects on the nervous system. *GUILLAIN-BARRÉ SYNDROME.* Guillain-Barré syndrome (see under Musculoskeletal and Nerve Disorders, p. 2406.1) has occasionally been reported after vaccination, although causal relationships have been difficult to evaluate.[1] Such reports have been made after diphtheria and tetanus vaccines (p. 2383.2), haemophilus influenzae vaccines (p. 2387.3), hepatitis A vaccines (p. 2389.1), hepatitis B vaccines (p. 2391.1), a swine influenza vaccine (p. 2395.1), measles, mumps, and rubella vaccines (p. 2401.1), meningococcal vaccines (p. 2402.2), oral poliomyelitis vaccines (p. 2411.3), and rabies vaccines (p. 2414.3); the evidence is strongest for the association with swine influenza vaccine.

1. Haber P, *et al.* Vaccines and Guillain-Barré syndrome. *Drug Safety* 2009; 32: 309–23.

Precautions

Most persons can safely receive the majority of vaccines. In a few individuals vaccination is contra-indicated or should be deferred.

All vaccines are contra-indicated in those who have had a previous confirmed anaphylactic reaction to a previous dose of a vaccine containing the same antigens or a confirmed anaphylactic reaction to another component contained in the relevant vaccine (for example, neomycin, polymyxin B, or streptomycin which may be present in trace amounts).

Some vaccines are prepared in egg cultures and are contra-indicated in persons with a confirmed anaphylactic reaction to egg.

Live vaccines are contra-indicated in immunosuppressed patients in these situations:

- severe primary immunodeficiency
- malignant disease being treated with either chemotherapy or radiotherapy and for at least 6 months after stopping such treatment
- solid organ transplant receiving immunosuppressive therapy
- bone marrow transplant during, and for at least 12 months after stopping, immunosuppressive therapy (or longer if graft-versus-host disease develops)
- all patients receiving high-dose systemic corticosteroids until at least 3 months after stopping treatment; this includes children receiving prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2 mg/kg for at least 1 week or 1 mg/kg for 1 month and adults receiving a daily dose of 40 mg for more than 1 week.
- HIV positive patients with immunosuppression

Vaccination may be delayed in persons who are acutely unwell and in those with evolving neurological conditions (until stabilised). In pregnancy, vaccination should be delayed until after delivery; termination of pregnancy is not recommended if a vaccine is inadvertently given during pregnancy.

If any alcohol or disinfectant is used for cleansing the skin it should be allowed to evaporate before vaccination otherwise inactivation of live vaccines may occur.

Immunocompromised patients. For a discussion of the use of vaccines in HIV-infected and otherwise immunocompromised patients, see under Uses, p. 2374.3.

Premature infants. In the UK, the Royal College of Paediatrics and Child Health[1] and the Department of Health[2] consider that all routine childhood immunisations should be scheduled on the basis of the child's actual date of birth with no allowance being made for prematurity. In the USA, the American Academy of Pediatrics offers similar advice.[3] It is acknowledged that more studies are required into immunisation in prematurity, particularly in infants receiving corticosteroids.[1] There is some evidence that a minority of premature infants may fail to respond adequately to Haemophilus influenzae vaccines and to hepatitis B immunisation.[1] It has also been suggested that there may be an increased risk of apnoea and bradycardia in premature infants vaccinated with polyvalent vaccines,[4,5] and some licensed product information for pentavalent or hexavalent vaccines has been amended accordingly.

1. Royal College of Paediatrics and Child Health. Immunisation of the immunocompromised child: best practice statement February 2002. Available at: http://www.rcpch.ac.uk/doc.aspx?id_Resource=1768 (accessed 27/08/10)
2. DoH. *Immunisation Against Infectious Disease* 2006 (updated 17th July, 2013): "The Green Book". Available at: https://www.gov.uk/government/publications/green-book-the-complete-currentedition (accessed 09/09/13)
3. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2013.
4. Schulzke S, *et al.* Apnoea and bradycardia in preterm infants following immunisation with pentavalent or hexavalent vaccines. *Eur J Pediatr* 2005; 164: 432–5.
5. Cooper PA, *et al.* Apnea and its possible relationship to immunization in ex-premature infants. *Vaccine* 2008; 26: 3410–3.

Interactions

The ability of vaccines to induce an immune response can be influenced by the recent use of other vaccines or immunoglobulins. Live vaccines should either be given simultaneously (but at different sites) or an interval of at least 3 weeks allowed between them. Live vaccines should normally be given at least 3 weeks before or at least 3 months after the use of immunoglobulin. However, travellers should receive appropriate vaccines regardless of these limitations if time is short.

Patients receiving immunosuppressant therapy, including antineoplastics or therapeutic doses of corticosteroids, may also display a reduced response to vaccines and deferral of immunisation is advised, see Precautions, above. For further details on immunisation in immunocompromised patients, see under Uses and Administration, p. 2374.3.

Any agent that is active against the bacterial or viral strain present in the vaccine may interfere with development of a protective immune response but treatment with antibacterials is not a contra-indication to immunisation.

Adenovirus Vaccines

Profile

Adenovirus type 4 and type 7 vaccine is a live, oral vaccine used to prevent febrile acute respiratory disease caused by adenovirus types 4 and 7. It is approved in the US for use in military personnel from 17 to 50 years of age. A single vaccine dose is given orally as 2 tablets; one tablet of adenovirus type 4 and one of adenovirus type 7. The tablets should be swallowed whole to avoid releasing the virus in the upper respiratory tract. The virus can be shed in the stool for up to 28 days after vaccination; proper personal hygiene should be followed during this period to reduce the risk of viral transmission.

The vaccine should not be given to pregnant women and pregnancy should be avoided for 6 weeks after receiving the vaccine. Vaccination should also be postponed in those with vomiting and/or diarrhoea.

References.
1. Hoke CH, Snyder CE. History of the restoration of adenovirus type 4 and type 7 vaccine, live oral (Adenovirus Vaccine) in the context of the Department of Defense acquisition system. *Vaccine* 2013;.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: An Ke Rui (安柯瑞).

AIDS Vaccines

HIV Vaccines; Vacunas contra VIH; Vacunas del SIDA.

Profile

Many prototype vaccines against AIDS have been or are being developed but the results of clinical studies have generally been disappointing.

Despite the passage of more than two decades since the discovery of HIV, no effective vaccine has been found to either ameliorate the disease or to prevent infection.[1-14] Globally tens of millions of people are infected with HIV, with the overwhelming majority of infections occurring in developing countries that in many cases lack the resources and infrastructure to acquire and deliver costly antiretroviral therapy. A safe, effective, easily administered, and inexpensive AIDS vaccine is therefore desperately required.

There are many reasons why no such vaccine has so far been developed. Firstly, natural infection with HIV does not result in protective immunity; rather, it establishes persistent and lifelong infection and viral clearance and development of resistance to re-infection never occur. This means that there is no model of protective immunity to emulate through vaccination. Various aspects of the biology of the virus have also presented thus far insurmountable problems in vaccine development. The complex structure of the HIV envelope glycoprotein is inherently resistant to antibody attack and the virus has the capacity to evolve quickly in order to evade any neutralising antibody responses mounted by the host. In addition, the selective infection, progressive destruction, and impaired regeneration of CD4+ T helper cells, and the enormous genetic diversity of HIV with its continually evolving geographical distribution and prevalence have proven problematical. Finally, the ability of HIV to evade immune surveillance enables it to establish a state of proviral latency in long-lived CD4+ cells thus providing a persistent, yet immunologically invisible, reservoir of virus infection.

Despite these problems, research has continued[1-9,15] into developing AIDS vaccines from two distinct perspectives, namely prophylactic vaccines aimed at preventing primary infection and therapeutic vaccines aimed at reducing the rate of disease progression in HIV-infected individuals. Subunit recombinant viral envelope proteins, notably gp120, have been investigated as both prophylactic and therapeutic vaccines, but phase III clinical studies have proved disappointing.[9] In one, involving a bivalent formulation of recombinant gp120 proteins from HIV subtype B, predominant in North America and Europe (AIDSVAX B/B) given to 5009 subjects most of whom were homosexual men, no effect on the rate of HIV infection was found. In a second study in Thailand using AIDSVAX B/E, a related vaccine consisting of recombinant gp120 proteins from HIV subtypes B and E predominant in South-East Asia, no protection against HIV infection was found among 2546 HIV-negative injection drug users.[9] Despite these disappointing results, AIDSVAX B/E was evaluated in a further large study in a Thai population at community risk for HIV infection as the booster component of a combination immunisation prime-boost regimen that includes an attenuated canarypox vector prime (ALVAC vCP1521).[14] This regimen showed only a modest benefit with a trend toward reducing the risk of HIV infection but did not affect the early viral load or CD4+ T lymphocyte count in those who eventually became infected with HIV.

While typical HIV neutralising antibody responses are only transiently effective within a given individual and generally not cross-reactive with other isolates, several monoclonal antibodies have been derived from B cells or molecular clones of immunoglobulin genes obtained from HIV-infected persons during the course of natural infection, and have significant neutralisation activity against a wider array of HIV isolates. These monoclonal antibodies act by penetrating gp120 and other viral envelope proteins, thereby preventing CD4 attachment to the virus. Since they have activity against a broader range of isolates and may be produced in relatively large quantities by recombinant technology, passive delivery of a cocktail of monoclonal antibodies is being studied in *animal* models as a means of prophylaxis.[9] The cost of this approach may, however, potentially prohibit its future use on a wide scale in humans.

Efforts at understanding why it is so difficult to configure immunogens from the HIV envelope that more effectively elicit neutralising antibody responses continue but, in addition, attention has turned to what is termed the cytotoxic T lymphocyte (CTL) hypothesis.[9] This proposes that vaccination of uninfected individuals will not prevent infection but will induce an anti-HIV CTL (CD8+) response. If subsequently infected with HIV these immunised persons would be better able to control viral replication and progress to AIDS much more slowly or perhaps not at all and potentially decrease viral transmission. The validity of this hypothesis is at present uncertain but it has been supported by the observation of low level, yet detectable, HIV-specific CD8+ T cell responses in certain cohorts of highly exposed but uninfected individuals.

Additionally, new vaccine strategies are becoming available which it is thought will probably be able to elicit HIV-specific CTL responses of sufficient magnitude to allow direct testing of the concept in humans. Numerous *animal* studies are underway to assess the safety and immunogenicity of various replication-defective recombinant viral vectors (modified vaccinia Ankara strain, vesicular stomatitis virus, Venezuelan equine encephalitis virus, adeno-associated virus, and adenovirus) and also bacterial, yeast, and plasmid DNA vectors, all of which are designed to elicit antiviral CD8+ T cell responses.[9] However, initial analyses from a large study of an adenovirus-based vaccine designed to boost T cell responses (the STEP trial) provoked alarm since results suggested that it did not decrease susceptibility to HIV infection and might have increased it in some cases.[16] Final analysis of this study found that the vaccine did not prevent HIV-1 infection or reduce early viral levels.[17]

Recombinant plasmid DNA immunogens are also under investigation as potential AIDS vaccines because of their desirable safety profile and ability to express defined and discrete inserted HIV antigens. They are either used singly or as a priming immunogen in prime-boost regimens using different vaccine vectors for sequential immunisation. Initial results in preclinical *animal* studies were encouraging, but results have been disappointing in subsequent phase I human studies.[8]

Within the field of AIDS vaccine research, the decision to advance candidate vaccines from phase I or II to phase III efficacy studies is somewhat complex. At present there are no consistent criteria in place to provide guidance on such decisions and there is a need for a coordinated, objective, and rigorous process for prioritisation in order to facilitate vaccine development. To the same end, alternative designs for phase III studies are being considered, including the use of end-points such as reduction of viral load or preservation of CD4+ T cell counts for assessing vaccine efficacy rather than prevention of infection as the single primary end-point. These and other measures may facilitate licensure of vaccines which currently would not occur.

1. Esparza J, Bhamarapravati N. Accelerating the development and future availability of HIV-1 vaccines: why, when, where, and how? *Lancet* 2000; 355: 2061–6.
2. Hanke T. Prospect of a prophylactic vaccine for HIV. *Br Med Bull* 2001; 58: 205–18.
3. Makgoba MW, *et al.* The search for an HIV vaccine. *BMJ* 2002; 324: 211–13.
4. Weidle PJ, *et al.* HIV/AIDS treatment and HIV vaccines for Africa. *Lancet* 2002; 359: 2261–7.
5. Tramont EC, Johnston MI. Progress in the development of an HIV vaccine. *Expert Opin Emerg Drugs* 2003; 8: 37–45.
6. Stevceva L, Strober W. Mucosal HIV vaccines: where are we now? *Curr HIV Res* 2004; 2: 1–10.
7. Kinloch-de Loes S. Role of therapeutic vaccines in the control of HIV-1. *J Antimicrob Chemother* 2004; 53: 562–6.
8. Giri M, *et al.* DNA vaccines against human immunodeficiency virus type 1 in the past decade. *Clin Microbiol Rev* 2004; 17: 370–89.
9. Garber DA, *et al.* Prospects for an AIDS vaccine: three big questions, no easy answers. *Lancet Infect Dis* 2004; 4: 397–413.
10. Duerr A, *et al.* HIV vaccines: new frontiers in vaccine development. *Clin Infect Dis* 2006; 43: 500–11.
11. Robinson HL. HIV/AIDS vaccines: 2007. *Clin Pharmacol Ther* 2007; 82: 686–93.
12. Johnston MI, Fauci AS. An HIV vaccine–evolving concepts. *N Engl J Med* 2007; 356: 2073–81.
13. Kawalekar OU, *et al.* Current strategies and limitations of HIV vaccines. *Curr Opin Investig Drugs* 2010; 11: 192–202.
14. Rerks-Ngarm S, *et al.* Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009; 361: 2209–20.
15. Bansal GP, *et al.* Future paths for HIV vaccine research: exploiting results from recent clinical trials and current scientific advances. *Curr Opin Mol Ther* 2010; 12: 39–46.
16. Sekaly R-P. The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development? *J Exp Med* 2008; 205: 7–12.
17. Buchbinder SP, *et al.* Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet* 2008; 372: 1881–93.

Anthrax Vaccines

Vacunas del carbunco.
ATC — J07AC01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Anthrax Vaccine for Human Use (Adsorbed, Prepared from Culture Filtrates)); Vaccinum Anthracis Adsorbatum ab Colato Culturarum ad Usum Humanum. A preparation of *Bacillus anthracis* antigens precipitated by aluminium potassium sulfate. The antigens are prepared from a sterile culture filtrate produced by a non-encapsulated strain, either avirulent or attenuated, of *B. anthracis*. The main virulence components of *B. anthracis* are the polyglutamic acid capsule and 2 binary anthrax toxins, namely lethal toxin and oedema toxin, formed from the respective combination of protective antigen with either lethal factor or oedema factor. In addition, the vaccine is likely to contain many other *B. anthracis* antigens, including membrane proteins, secreted proteins, cytoplasmic proteins, peptidoglycans, nucleic acids, and carbohydrates. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

An anthrax vaccine that is an alum precipitate of the antigen found in the sterile filtrate of suitable cultures of the Sterne strain of *Bacillus anthracis* is available in the UK for human use. It is used for active immunisation against anthrax (p. 173.2) and is recommended as *pre-exposure prophylaxis* for persons working with potentially infected animals or animal products. It is given in 4 doses, each of 0.5 mL by intramuscular injection. The first 3 doses are separated by intervals of 3 weeks and the fourth dose follows after an interval of 6 months; reinforcing doses of 0.5 mL are required each year. In the USA, an anthrax vaccine was originally licensed for subcutaneous use as a series of 6 doses given at 0, 2, and 4 weeks and 6, 12, and 18 months followed by yearly booster doses. In December 2008, the FDA approved a series of 5 intramuscular doses, each of 0.5 mL, given at 0 and 4 weeks and 6, 12, and 18 months; reinforcing doses of 0.5 mL are required at yearly intervals after the 18-month dose. Those with medical contraindications to intramuscular injections may be given the vaccine by the original 6-dose subcutaneous regimen. For *post-exposure prophylaxis* the FDA recommends that 3 doses of the vaccine, each of 0.5 mL, may be given subcutaneously at 0, 2, and 4 weeks in addition to recommended antibacterial therapy.

References.
1. CDC. Use of anthrax vaccine in response to terrorism: supplemental recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2002; 51: 1024–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5145a4.htm (accessed 27/08/10)
2. Health Protection Agency. Guidelines for action in the event of a deliberate release: anthrax. Version 5.9, 16 April 2007. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947401128 (accessed 15/07/08)
3. Grabenstein JD. Countering anthrax: vaccines and immunoglobulins. *Clin Infect Dis* 2008; 46: 129–36.
4. Donegan S, *et al.* Vaccines for preventing anthrax. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 01/12/09).
5. CDC. Use of anthrax vaccine in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR* 2010; 59 (RR-6): 1–30. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5906.pdf (accessed 26/07/10)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Biothrax.

Pharmacopoeial Preparations
Ph. Eur.: Anthrax Vaccine for Human Use (Adsorbed, Prepared from Culture Filtrates);
USP 36: Anthrax Vaccine Adsorbed.

Anti-D Immunoglobulins

Immunoglobulinas anti-D; Immunoglobulinas anti-D; Immunoglobulinas anti Rh.

ATC — J06BB01.

UNII — 48W7181FLP (human Rh_o (D) immune globulin).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Anti-D Immunoglobulin; Immunoglobulinum Humanum Anti-D; Anti-D (Rh_o) Immunoglobulin BP 2014). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is intended for intramuscular administration. It is obtained from plasma from D-negative donors who have been immunised against the D-antigen. It contains specific antibodies against the erythrocyte D-antigen and may also contain small quantities of other blood group antibodies, such as anti-C, anti-E, anti-A, and anti-B. Normal immunoglobulin may be added. The liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored in an airtight container.

Ph. Eur. 8: (Human Anti-D Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Anti-D ad Usum Intravenosum; Anti-D Immunoglobulin for Intravenous Use BP 2014). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from D-negative donors who have been immunised against the D-antigen. It contains specific antibodies against the erythrocyte D-antigen and may also contain small quantities of other blood group antibodies. Human normal immunoglobulin for intravenous administration may be added. Storage requirements are similar to those for Human Anti-D Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25 degrees.

USP 36: (Rh_o (D) Immune Globulin). A sterile solution of globulins derived from human plasma containing antibody to the erythrocyte factor Rh_o (D). It contains 10 to 18% of protein, of which not less than 90% is gamma globulin. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Anti-D immunoglobulin is used to prevent a rhesus-negative mother actively forming antibodies to fetal rhesus-positive red blood cells that may pass into the maternal circulation during childbirth, abortion, or certain other sensitising events. In subsequent rhesus-positive pregnancies these antibodies could produce haemolytic disease of the newborn (erythroblastosis foetalis). The injection of anti-D immunoglobulin is not effective once the mother has formed anti-D antibodies. Anti-D immunoglobulin is also used in the management of some blood disorders, mainly immune thrombocytopenia.

Anti-D immunoglobulin products are available either for intramuscular use only or for intramuscular or intravenous use. Doses differ for these products and the manufacturer's recommendation should be followed for commercial products.

In the UK, recommendations produced by expert groups relate to the use of a non-proprietary product produced by the National Blood Transfusion Service. They recommend that **postnatal prophylaxis** with anti-D immunoglobulin should always be given to rhesus-negative mothers with no anti-D antibodies in their serum and who have just delivered rhesus-positive infants. It should be given as soon as possible after delivery but may give some protection even if treatment is delayed beyond 72 hours. A dose of 500 units (100 micrograms) by intramuscular injection will clear up to 4 mL of fetal red cells. An additional dose may be required depending on the amount of transplacental bleeding; for bleeds exceeding 4 mL an additional 125 units for each mL of red cells will be required.

For routine **antenatal prophylaxis**, two intramuscular doses of either 500 units or 1000 to 1650 units of anti-D immunoglobulin should be given at 28 and 34 weeks' gestation; alternatively a single dose of 1500 units may be given between 28 and 30 weeks gestation. Doses given depend on the preparation used. Postnatal prophylaxis is still necessary.

There is also a risk of sensitisation during pregnancy from spontaneous, induced, or threatened abortion, amniocentesis, or external version. Any rhesus-negative woman at **risk of transplacental haemorrhage** during pregnancy and not known to be sensitised should be given an intramuscular dose of 250 units at up to 20 weeks' gestation and 500 units of anti-D immunoglobulin after 20 weeks' gestation.

Anti-D immunoglobulin is also given to rhesus-negative women of child-bearing potential after the inadvertent **transfusion of Rh-incompatible blood**, or after receiving blood components containing rhesus-positive red cells or organ donations from rhesus-positive donors. The dose is based on the amount of red blood cells transfused; an intramuscular dose up to 125 units/mL of transfused cells may be used.

For **immune thrombocytopenia** (idiopathic thrombocytopenic purpura), a usual initial dose of 250 units/kg (50 micrograms/kg) of a licensed anti-D immunoglobulin product is given by intravenous injection; it may be given in two divided doses on separate days if desired. Maintenance doses usually range between 125 to 300 units/kg (25 to 60 micrograms/kg) depending on the clinical response. A reduced initial dose of 125 to 200 units/kg (25 to 40 micrograms/kg) is recommended in patients with pre-existing anaemia (haemoglobin below 10 g/dL).

Haemolytic disease of the newborn. Rhesus (Rh) incompatibility, in particular Rh(D) incompatibility, is a major cause of potentially severe haemolytic disease of the newborn,[1] although other blood group antibodies may also cause the disease. The use of anti-D immunoglobulin to suppress the production of anti-D antibodies in a Rh(D)-negative mother in response to leakage of red blood cells across the placenta from a Rh(D)-positive fetus has produced a major reduction in the incidence of this disorder.

Prophylaxis. Postnatal prophylaxis of Rh(D)-negative mothers after the birth of a Rh(D)-positive infant is well established. In 1971, WHO[2] suggested a standard intramuscular dose of 200 to 300 micrograms but stated that a 100-microgram dose was likely to have a success rate only slightly inferior to that of a 200-microgram dose, thus allowing optimum use to be made of a limited resource. Clinical experience in the UK has confirmed the efficacy of the 100-microgram (500 units) intramuscular dose and this is the amount officially recommended in the UK in such situations.[3,4] Doses do, however, vary considerably in other countries.

Despite the success of anti-D immunoglobulin prophylaxis, sensitisations have continued to occur. There are several possible reasons for this, the main one being immunisation during pregnancy where there has been no overt sensitising event. Postpartum doses may be omitted due to oversight or loss to follow-up. Assessment of the volume of any transplacental haemorrhage is essential to avoid inadequate dosing. Significantly large feto-maternal haemorrhage is likely to occur after traumatic deliveries including caesarean section, manual removal of the placenta, still-birth or intra-uterine death, abdominal trauma during the third trimester, delivery of twins, or unexplained hydrops fetalis.

The efficacy of postpartum prophylaxis is not in question but opinions differ on the need for prophylaxis during pregnancy. It is generally agreed that prophylaxis is necessary in all non-sensitised Rh(D)-negative women after therapeutic terminations at any stage of pregnancy, including medical termination utilising mifepristone, after ectopic pregnancy, spontaneous complete or incomplete miscarriage after 12 weeks' gestation, or threatened miscarriage after 12 weeks' gestation as evidenced by abnormal bleeding or abdominal pain. Recommendations have been made by the British Committee for Standards in Haematology for the management of these sensitising events.[4]

Prophylaxis should also be given to all non-sensitised Rh (D)-negative women after the following sensitising events during pregnancy: invasive prenatal diagnosis including amniocentesis, chorion villus sampling, or fetal blood sampling; other intra-uterine procedures such as insertion of shunts or embryo reduction; antepartum haemorrhage; external cephalic version of the fetus; closed abdominal injury; or intra-uterine death.[3,4] A dose of 50 micrograms (250 units) is recommended for prophylaxis after these events up to 20 weeks of pregnancy, and at least 100 micrograms (500 units) thereafter.

In the UK routine antenatal prophylaxis at 28 and 34 weeks' gestation is recommended for all Rh(D)-negative women[3-5] and should be given irrespective of whether anti-D prophylaxis had been given for other sensitising events during the same pregnancy or previous pregnancies.[4]

Treatment. In mild cases, the resultant hyperbilirubinaemia can be managed with phototherapy. In severe cases, exchange transfusions may be necessary and intra-uterine transfusions may be considered in pregnancies of less than about 34 weeks' gestation; beyond this, premature delivery is often preferable.[6] Some clinicians have reported treatment failures with intra-uterine transfusions but have found intravenous normal immunoglobulin 400 mg/kg daily for 5 days every 2 to 3 weeks to the mother to be effective. There are several case reports[7,8] of beneficial responses using similar doses, but no benefit was seen in 4 patients receiving 1000 mg/kg once a week.[9] This dose, however, appeared to reduce the severity of the disease in a patient with Kell sensitisation.[9] Reductions in bilirubin concentrations have been reported with intravenous normal immunoglobulin 500 mg/kg as a single dose in newborn infants,[10] and a systematic review[11] found that such treatment reduced the number of infants requiring exchange transfusion and the duration of hospital stay and phototherapy needed. Reports in small numbers of infants[12-16] suggest that epoetins may be of value in controlling anaemia which develops 2 to 8 weeks after birth.

1. Regan F, *et al.* Haemolytic disease of the newborn and its prevention. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 27–32.
2. WHO. Prevention of Rh sensitization: report of a WHO scientific group. *WHO Tech Rep Ser 468* 1971. Also available at: http://libdoc.who.int/trs/WHO_TRS_468.pdf (accessed 03/10/07)
3. McClelland DBL, ed. *Handbook of transfusion medicine: Blood Transfusion Services of the United Kingdom.* 4th ed. London: The Stationery Office, 2007. Also available at: http://www.transfusionguidelines.org.uk/docs/pdfs/htm_edition-4_all-pages.pdf (accessed 02/10/07)
4. Parker J, *et al.* Guidelines for the use of prophylactic anti-D immunoglobulin: British Committee for Standards in Haematology. (issued 5th December, 2006; awaiting update). Available at: http://www.bcshguidelines.com/pdf/Anti-D_070606.pdf (accessed 27/08/10)
5. NICE. Routine antenatal anti-D prophylaxis for women who are rhesus D negative: review of NICE technology appraisal guidance 41 (issued August 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA156Guidance.pdf (accessed 16/11/09)
6. Whittle MJ. Rhesus haemolytic disease. *Arch Dis Child* 1992; 67: 65–8.
7. Berlin G, *et al.* Rhesus haemolytic disease treated with high-dose intravenous immunoglobulin. *Lancet* 1985; i: 1153.
8. de la Cámara C, *et al.* High-dose intravenous immunoglobulin as the sole prenatal treatment for severe Rh immunization. *N Engl J Med* 1988; 318: 519–20.
9. Chitkara U, *et al.* High-dose intravenous gamma globulin: does it have a role in the treatment of severe erythroblastosis fetalis? *Obstet Gynecol* 1990; 76: 703–8.
10. Rübo J, *et al.* High-dose intravenous immune globulin therapy for hyperbilirubinemia caused by Rh hemolytic disease. *J Pediatr* 1992; 121: 93–7.
11. Gottstein R, Cooke RWI. Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F6–F10.
12. Ohls RK, *et al.* Recombinant erythropoietin as treatment for the late hyporegenerative anemia of Rh hemolytic disease. *Pediatrics* 1992; 90: 678–80.
13. Scaradavou A, *et al.* Suppression of erythropoiesis by intrauterine transfusions in hemolytic disease of the newborn: use of erythropoietin to treat the late anemia. *J Pediatr* 1993; 123: 279–84.
14. Ovall F, *et al.* Management of late anemia in Rhesus hemolytic disease: use of recombinant human erythropoietin (a pilot study). *Pediatr Res* 1996; 39: 831–4.
15. Zuppa AA, *et al.* Recombinant erythropoietin in the prevention of late anaemia in intrauterine transfused neonates with Rh-haemolytic disease. *Fetal Diagn Ther* 1999; 14: 270–4.
16. Dhodapkar KM, Blei F. Treatment of hemolytic disease of the newborn caused by anti-Kell antibody with recombinant erythropoietin. *J Pediatr Hematol Oncol* 2001; 23: 69–70.

Immune thrombocytopenia. Normal immunoglobulin is used for immune thrombocytopenia (p. 1606.1), and anti-D immunoglobulin has been found to have similar properties. The potential role of anti-D immunoglobulin in the treatment of immune thrombocytopenia has been discussed in several reviews.[1-3] In general, despite many studies showing the clinical efficacy and low toxicity of intravenous anti-D immunoglobulin, its precise role has not been defined for several reasons. Firstly, the optimal dose has not been established: doses used have ranged from 12.5 to 25 micrograms/kg daily, given for at least 2 days, in early studies to later more promising single doses of 50 to 75 micrograms/kg. Secondly, no study has shown anti-D immunoglobulin to be as effective as corticosteroid therapy for initial treatment. Furthermore, despite suggestions that anti-D immunoglobulin may be safer and easier to give than normal immunoglobulin, good comparative data are scanty. Clinical studies have, however, shown the safety and efficacy of intravenous anti-D immunoglobulin in Rh(D)-positive, non-splenectomised patients with immune thrombocytopenia.[1] A prospective, randomised clinical study[4] in Rh(D)-positive children with immune thrombocytopenia found that a single intravenous dose of 75 micrograms/kg raised the platelet count more rapidly than a single intravenous dose of 50 micrograms/kg, and was as effective as a single intravenous dose of 800 mg/kg of normal immunoglobulin.

1. Scaradavou A, Bussel JB. Clinical experience with anti-D in the treatment of idiopathic thrombocytopenic purpura. *Semin Hematol* 1998; 35 (suppl 1): 52–7.
2. Sandler SG. Treating immune thrombocytopenic purpura and preventing Rh alloimmunization using intravenous rho (D) immune globulin. *Transfus Med Rev* 2001; 15: 67–76.
3. Sandler SG. Intravenous Rh immune globulin for treating immune thrombocytopenic purpura. *Curr Opin Hematol* 2001; 8: 417–20. Correction. *ibid.* 2002; 9: 179.
4. Tarantino MD, *et al.* Single dose of anti-D immune globulin at 75 μ g/kg is as effective as intravenous immune globulin at rapidly raising the platelet count in newly diagnosed immune thrombocytopenic purpura in children. *J Pediatr* 2006; 148: 489–94.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

In patients given anti-D immunoglobulin for immune thrombocytopenia (ITP) there have been rare reports of back pain, shaking chills, fever, and discoloured urine; such signs and symptoms may be associated with intravascular haemolysis. Serious and sometimes fatal complications of intravascular haemolysis including anaemia, acute renal insufficiency, or disseminated intravascular coagulation have been rarely reported. Most reported cases of

haemolysis occurred within 4 hours of the dose; fatal outcomes and complications occurred most frequently in patients more than 65 years of age with comorbid conditions. Patients should be closely monitored for at least 8 hours after a dose of anti-D immunoglobulin.

For the treatment of ITP, anti-D immunoglobulin is contra-indicated in rhesus-negative or splenectomised patients. Patients with ITP who need a blood transfusion should be given rhesus-negative red blood cells so as not to exacerbate ongoing haemolysis. Those with low initial haemoglobin concentrations (less than 10 g/dL) should be given a reduced dosage of the immunoglobulin to minimise the risk of severe anaemia.

When given for prophylaxis of rhesus sensitisation, anti-D immunoglobulin should not be used in rhesus-positive individuals.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies anti-D immunoglobulin 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

As for immunoglobulins in general, p. 2373.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Igantid; Immunorho; Kam Rho-D; Partoben; Partogamma; Rhesogamma; Rhophylac; ***Austral.***: WinRho; ***Austria***: Partobulin; Rhesogam†; Rhophylac; ***Belg.***: RhoGAM; WinRho†; ***Braz.***: Matergam†; Partogama; Rhesonativ; Rhophylac; ***Canad.***: HyperRho S/D†; WinRho; ***Chile***: Igamad; Immunorho; Rhesogamma P†; ***Cz.***: Igamad; Partobulin; Rhesonativ; Rhophylac; ***Denm.***: Rhesonativ; Rhophylac; ***Fin.***: Rhesonativ; Rhophylac; ***Fr.***: Rhophylac; ***Ger.***: Partobulin†; Rhesonativ; Rhophylac; ***Gr.***: Rhesogamma P; Rhesuman; Rhophylac; WinRho; ***Hong Kong***: HyperRho-D; Partobulin; RhoGAM; WinRho; ***Hung.***: Rhesonativ; RhoGAM†; Rhophylac; ***India***: Anti-D; Matergam-P; Micrhogam; ***Indon.***: HyperRho S/D; ***Irl.***: Rhesonativ; Rhophylac; ***Israel***: BayRho-D†; KamRho-D; Rhophylac; WinRho; ***Ital.***: Igamad; Immunorho; Partobulin; Rhophylac; WinRho†; ***Mex.***: Octaglob D; Rhesogamma P; Rhophylac; ***Neth.***: RheDQuin; Rhesonativ; Rhophylac; WinRho†; ***Norw.***: Rhesonativ; Rhophylac; ***NZ***: RhoGAM; WinRho; ***Philipp.***: WinRho; ***Pol.***: Gamma Anty D; Partobulin; Rhesonativ; Rhophylac; ***Port.***: Rhesonativ; Rhophylac; WinRho†; ***Rus.***: HyperRho S/D (ГиперРОУ С/Д); Immunoro (Иммунорро); KamRHO (КамРОУ); Partobulin (Партобулин); Rhesonativ (Резонатив); ***S.Afr.***: Rhesugam; ***Singapore***: WinRho†; ***Spain***: Gamma Anti D†; Igamad; Rhesogamma†; Rhophylac; ***Swed.***: Rhesonativ; Rhophylac; ***Switz.***: Rhophylac; ***Thai.***: Igamad; Rhesonativ; ***Turk.***: BayRho-D; HyperRho-D; Immunorho; Partobulin; Rhesogamma P; Rhesuman; RhoGAM; Rhophylac; WinRho; ***UK***: D-Gam; Partobulin; Rhophylac; WinRho†; ***USA***: HyperRho S/D; MICRhoGAM; RhoGAM; Rhophylac; WinRho.

Pharmacopoeial Preparations
Ph. Eur.: Human Anti-D Immunoglobulin for Intravenous Administration; Human Anti-D Immunoglobulin;
USP 36: Rh_o (D) Immune Globulin.

Argentine Haemorrhagic Fever Vaccines

Junin Haemorrhagic Fever Vaccines; Vacunas de la fiebre hemorrágica argentina.

Profile

A live attenuated vaccine has been investigated for active immunisation against Argentine haemorrhagic fever.

References.
1. Maiztegui JI, *et al.* Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. *J Infect Dis* 1998; 177: 277–83.
2. Petuillade MR, Enría DA. Análisis de la utilidad de la vacuna Candid 1 en la prevención de la fiebre hemorrágica argentina en niños. *Rev Panam Salud Publica* 2005; 18: 100–106.

BCG Vaccines

Bacillus Calmette-Guérin Vaccines; Vacunas BCG; Вакцины БЦЖ.

ATC — J07AN01; L03AX03.

UNII — 08Q62LY3KF (bacillus calmette-guerin live (attenuated) antigen); 5HS854U8MZ (bacillus calmette-guerin live antigen, B)

Pharmacopoeias. Many pharmacopoeias, including *Br., Eur.* (see p. vii), and *US*, have monographs.

Ph. Eur. 8: (BCG Vaccine, Freeze-dried; Vaccinum Tuberculosis (BCG) Cryodesiccatum; Bacillus Calmette-Guérin Vaccine BP 2014). A freeze-dried preparation containing live bacteria obtained from a strain derived from the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity to protect against tuberculosis has been established. It may contain a stabiliser. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from direct sunlight.

The BP 2014 states that BCG may be used on the label.

The BP 2014 gives BCG Vaccine as an approved synonym.

BP 2014: (Percutaneous Bacillus Calmette-Guérin Vaccine). A suspension of living cells of an authentic strain of the bacillus of Calmette and Guérin with a higher viable bacterial count than Bacillus Calmette-Guérin Vaccine. It is supplied as a dried vaccine and is reconstituted immediately before use by the addition of a suitable sterile liquid. The dried vaccine should be stored at a temperature below -20 degrees and be protected from light.

The BP 2014 states that Tub/Vac/BCG (Perc) may be used on the label.

The BP 2014 gives Percut. BCG Vaccine as an approved synonym.

USP 36: (BCG Vaccine). A dried living culture of the bacillus Calmette-Guérin strain of *Mycobacterium tuberculosis* var. *bovis*; it is grown from a strain that has been maintained to preserve its capacity for conferring immunity. It contains an amount of viable bacteria such that inoculation, in the recommended dose, of tuberculin-negative persons results in an acceptable tuberculin conversion rate. It contains a suitable stabiliser and no antimicrobial agent. The dried vaccine should be stored in hermetically sealed containers at 2 degrees to 8 degrees. The reconstituted vaccine should be used immediately after preparation and any portion not used within 2 hours should be discarded.

Ph. Eur. 8: (BCG for Immunotherapy; BCG ad Immunocurationem). A freeze-dried preparation of live bacteria derived from a culture of the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity for treatment has been established. It may contain a stabiliser. The product should be stored at 2 degrees to 8 degrees and be protected from direct sunlight.

USP 36: (BCG Live). A freeze-dried preparation of attenuated live bacteria derived from a culture of Bacillus Calmette-Guérin (*Mycobacterium bovis*, var. BCG) for intravesical use only. It is reconstituted and further diluted aseptically with a sterile diluent before use. A reconstituted dose contains $1.0–19.2 \times 10^8$ colony-forming units (cfu). It does not contain a preservative.

BCG Live is sensitive to light and must be stored in a glass container, protected from direct light, and at 2 degrees to 8 degrees.

Uses and Administration

BCG vaccines are used for active immunisation against tuberculosis. A form suitable for immunotherapy is also used locally in the treatment and prophylaxis of carcinoma *in-situ* of the bladder, and the prophylaxis of recurrent early stage bladder papillomas after resection.

For vaccination against **tuberculosis** different strategies may be adopted, depending on the prevalence of the disease in local populations, the prevalence of HIV co-infection, the potential for infant exposure to these diseases, and the existence of infrastructure to diagnose infection and follow-up vaccinated persons. WHO considers that BCG vaccination of adults is not normally recommended, although it may be considered for tuberculin-negative subjects in unavoidable and close contact with drug-resistant tuberculosis. In countries with a high prevalence of tuberculosis, infant immunisation with a single dose of BCG as soon as possible after birth is ideally to be recommended. However, these populations tend to have a high prevalence of HIV infection as well, and BCG vaccination is contra-indicated in HIV-infected subjects. Nonetheless, WHO considers that children without HIV infection will particularly benefit from vaccination in these circumstances, and recommends that immunisation should be carried out in:
- infants born to women of unknown HIV status
- infants without obvious signs of HIV infection born to women known to be HIV-infected
- infants known to be HIV-negative as a result of virological testing

It considers that immunisation should be avoided in infants known to be infected with HIV, or whose HIV status is unknown but who are born to HIV-infected mothers and have signs or symptoms suggestive of HIV infection.

In contrast, a country such as the UK has a relatively low prevalence of tuberculosis, and routine immunisation is no longer carried out. Instead, immunisation is targeted at groups considered to be at increased risk:
- all neonates and infants (0 to 12 months) living in areas where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- all neonates and infants with a parent or grandparent born in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- previously unvaccinated children aged 1 to 5 years with a parent or grandparent born in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population; such children aged from 6 to 16 years should also be vaccinated if they have been shown to be tuberculin-negative
- previously unvaccinated, tuberculin-negative contacts of persons suffering from active respiratory tuberculosis
- previously unvaccinated, tuberculin-negative immigrants under 16 years of age who were born in, or lived in for at least 3 months, a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- previously unvaccinated, tuberculin-negative persons under 16 years of age intending to stay or work with local people for more than 3 months in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population.
- vaccination should be *withheld* in all those known or suspected to be HIV-infected, regardless of clinical status. Where vaccination is indicated, as in infants born to HIV-positive mothers, it should only be given after two appropriately timed negative postnatal tests for HIV infection.

Vaccination is also recommended in the UK for previously unvaccinated, tuberculin-negative persons under 35 years of age in the following groups:
- healthcare workers or laboratory staff at high risk of infection
- veterinary and other staff who handle animals known to be susceptible to tuberculosis
- staff in any institution where the incidence of tuberculosis is high

In the USA, CDC advises still more selective use, with BCG vaccination restricted essentially to tuberculin-negative children or health workers who are continually exposed to individuals with untreated or drug-resistant tuberculosis.

BCG vaccine is given intradermally (intracutaneously) at the insertion of the deltoid muscle in a dose of 0.1 mL; infants under 12 months of age are given 0.05 mL.

Contacts of patients with active pulmonary tuberculosis may require chemoprophylaxis (see under Tuberculosis, p. 210.2) despite previous vaccination. Neonates and children under 2 years of age should be given chemoprophylaxis and immunised, if appropriate, once the course is completed. An isoniazid-resistant form of the vaccine has been produced for use in patients who have received isoniazid, but its use is not recommended.

For use in immunotherapy of **bladder cancer** several regimens have been tried. A typical induction regimen consists of once-weekly intravesical instillation of a solution containing 1 to 16×10^8 colony forming units of BCG in about 50 mL of preservative-free saline 0.9%, for 6 consecutive weeks. Maintenance regimens vary widely from single doses or short courses (once a week for 3 weeks) at 3- to 6-monthly intervals, to instillation once a month; the period of suggested maintenance also varies from 6 months to 3 years. Some also favour a consolidation regimen of three further instillations, a week apart, carried out 6 weeks after completion of induction. Instillations should be retained in the bladder for 2 hours if possible, and then voided with the patient in a sitting position to minimise the risk of environmental contamination (see also Precautions, p. 2380.1).

References.
1. WHO. BCG vaccine: WHO position paper. *Wkly Epidem Rec* 2004; 79: 27–38. Also available at: http://www.who.int/immunization/wer7904BCG_Jan04_position_paper.pdf (accessed 23/06/10)

Leprosy. BCG vaccination has been shown to protect recipients against leprosy[1,2] and is considered to be one of the factors responsible for the decrease in the incidence of leprosy. One meta-analysis[1] of studies using BCG vaccine to prevent leprosy found that the average protective effect was 26% for the clinical studies and 61% for the observational (cohort or case-controlled) studies. Protection was better for multibacillary forms rather than paucibacillary forms of leprosy. Age at the time of vaccination was not a predictor of vaccine efficacy, but in the observational studies the protective effect was found to decrease with age. Clinical studies indicated that an additional dose of BCG was more effective than a single dose. For further details concerning the use of BCG vaccines in both the immunoprophylaxis and immunotherapy of leprosy, see Leprosy Vaccines, p. 2397.2.

1. Setia MS, *et al.* The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis* 2006; 6: 162–70.
2. Merle CSC, *et al.* BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. *Expert Rev Vaccines* 2010; 9: 209–22.

Malignant neoplasms. Immunotherapy with BCG vaccines has been tried in various malignant disorders and is most successful when given locally. The possibility that

BCG vaccination might protect children against malignancies has been discussed.[1]

1. Grange JM, Stanford JL. BCG vaccination and cancer. *Tubercle* 1990; 71: 61–4.

BLADDER. Immunotherapy with adjuvant intravesical BCG is used in the management of bladder cancers and is the treatment of choice for carcinoma *in situ* (p. 700.2), although debate about its exact role in non-muscle-invasive bladder cancer is ongoing.[1,2] It does not have a direct toxic effect on tumour cells, but produces a cascade of immune reactions that is reported to reduce tumour recurrence and disease progression. A systematic review[3] indicated that intravesical BCG after transurethral resection (TUR) reduced recurrence of Ta and T1 bladder cancers compared with TUR alone. Another systematic review[4] of intravesical therapy concluded that tumour recurrence was significantly reduced with BCG when compared with mitomycin C but only in patients at high risk of recurrence; there was no difference in terms of disease progression or survival. However, a meta-analysis[5] reported intravesical BCG to be better than mitomycin C in the prevention of tumour recurrences, particularly in those on BCG maintenance regime, irrespective of the risk of recurrence.

1. Ayres BE, *et al.* Is the role of intravesical bacillus Calmette-Guérin in non-muscle-invasive bladder cancer changing? *BJU Int* 2010; 105 (suppl 2): 8–13.
2. Gontero P, *et al.* The role of bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer. *Eur Urol* 2010; 57: 410–29.
3. Shelley M, *et al.* Intravesical bacillus Calmette-Guerin in Ta and T1 bladder cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 05/11/07).
4. Shelley M, *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 05/11/07).
5. Böhle A, *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol (Baltimore)* 2003; 169: 90–5.

SKIN. Several studies have reported that BCG vaccine injected into intradermal metastases of melanoma (p. 714.3) can result in regression of the injected, and sometimes also the uninjected nodules. BCG therapy has been disappointing for visceral metastases. Many anecdotal reports and nonrandomised studies have shown benefit from BCG vaccine as adjuvant therapy, but these results have not been confirmed in large randomised, controlled studies.[1,2]

1. Ho VC, Sober AJ. Therapy for cutaneous melanoma: an update. *J Am Acad Dermatol* 1990; 22: 159–76.
2. Agarwala SS, *et al.* Mature results of a phase III randomized trial of bacillus Calmette-Guerin (BCG) versus observation and BCG plus dacarbazine versus BCG in the adjuvant therapy of American Joint Committee on Cancer stage I-III melanoma (E1673): a trial of the Eastern Oncology Group. *Cancer* 2004; 100: 1692–8.

Tuberculosis. Studies from many parts of the world have evaluated the efficacy of BCG vaccine to protect against tuberculosis. Levels of protection have varied from 0 to over 80%.[1] Many explanations for such variability have been proposed: interaction with the immune response to other mycobacterial infections; antigenic, microbiological, or formulation differences between BCG vaccines; differences in the natural history of infection and disease; variations in host genetics or nutrition; or methodological differences between studies.[1,2] It has been noted that in general the efficacy of BCG vaccine in any region is proportional to its distance from the equator and this possibly reflects differences in exposure to environmental mycobacteria.[3] This could be the strongest influence on efficacy,[3] with the implication that BCG may be least effective in areas of the world where the risk of tuberculosis is greatest. BCG also appears to be more effective against systemic (miliary and meningitic tuberculosis) than against pulmonary tuberculosis. It is likely that BCG cannot produce complete protection against infection, and the development of new vaccines is ongoing.[4-6]

National policies of BCG vaccination vary widely. Some countries recommend routine vaccination; in others, such as the UK,[7] and USA[8] routine vaccination is no longer carried out and targeted immunisation aimed at infants and others at increased risk is performed (see Uses and Administration, p. 2378.2). Schedules throughout the world have varied from single intradermal vaccination at birth (as recommended by WHO),[9] to single vaccination at age 10 to 14, to repeated vaccination every few years (particularly in eastern Europe). The percutaneous route has been found to be as effective as the intradermal route.[10] These policy differences appear to be related as much to differences of opinion about the mechanism of action and efficacy of vaccines as to local differences in the epidemiology of tuberculosis.[1] WHO considers BCG vaccination to be an adjunct to case detection and treatment in the control of tuberculosis,[9,11] and recommends that neither tuberculin skin testing nor repeat vaccination should be used.

1. Fine PEM, Rodrigues LC. Modern vaccines: mycobacterial diseases. *Lancet* 1990; 335: 1016–20.
2. Fine PEM. BCG vaccination against tuberculosis and leprosy. *Br Med Bull* 1988; 44: 691–703.
3. Fine PEM. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet* 1995; 346: 1339–45. Correction. *ibid.*; 347: 340.
4. von Reyn CF, Vuola JM. New vaccines for the prevention of tuberculosis. *Clin Infect Dis* 2002; 35: 465–74.
5. Orme IM. Tuberculosis vaccines: current progress. *Drugs* 2005; 65: 2437–44.
6. Lambert PH, *et al.* New vaccines against tuberculosis. *Clin Chest Med* 2009; 30: 811–26.
7. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_07991772IdcService=GET_FILE&dID=1159748&Rendition=Web (accessed 15/07/08)
8. CDC. TB elimination: BCG vaccine. (Issued November 2008). Available at: http://www.cdc.gov/tb/publications/factsheets/prevention/BCG.pdf (accessed 26/08/10)
9. Anonymous. WHO statement on BCG revaccination for the prevention of tuberculosis. *Bull WHO* 1995; 73: 805–6.
10. Hawkridge A, *et al.* Efficacy of percutaneous versus intradermal BCG in the prevention of tuberculosis in South African infants: randomised trial. *BMJ* 2008; 337: 1275–8.
11. WHO. BCG vaccine. *Wkly Epidem Rec* 2004; 79: 27–38. Available at: http://www.who.int/entity/wer/2004/en/wer7904.pdf (accessed 01/11/07)

HIV-INFECTED PATIENTS. Like other live vaccines, BCG vaccine should not be given to immunocompromised patients, including patients with symptomatic HIV infection or AIDS. WHO[1] states that HIV prevalence is one of the factors that should be considered when determining local policies on BCG vaccination (see Uses and Administration, p. 2378.2), and recommends that infants with known or likely HIV infection should not be vaccinated because of the increased risk in this group (see Immunocompromised Patients under Precautions, p. 2380.1). In the UK and USA, BCG vaccination is also not recommended for HIV-positive patients.

1. WHO. Revised BCG vaccination guidelines for infants at risk for HIV infection. *Wkly Epidem Rec* 2007; 82: 193–6. Available at: http://www.who.int/wer/2007/wer8221.pdf (accessed 01/11/07)

Adverse Effects and Treatment

As for vaccines in general, p. 2375.1.

Serious adverse reactions to BCG vaccines used *for immunisation* against tuberculosis are rare, although the incidence may vary between strains. The normal therapeutic response involves induration and development of a lesion at the injection site, possibly with enlargement of local lymph nodes; this lesion may later ulcerate and heal over some months leaving a scar. In a few patients an exaggerated reaction, usually associated with overdose, inadvertent subcutaneous injection, or use in persons who are already tuberculin positive, may result in an abscess or discharging ulcer, or suppurative lymphadenitis. Non-specific systemic reactions may include fever and headache. Generalised reactions, possibly due to hypersensitivity, have been reported with a few fatalities. Disseminated BCG infection may occur and has also led to fatalities, particularly in immunocompromised patients. Disseminated BCG complications such as osteitis have been reported with some BCG vaccines. Very rarely, a lupoid type of reaction has occurred, mostly after multiple revaccination.

Intravesical use of BCG in the treatment and prophylaxis of bladder cancer is associated with an inflammatory response; transient dysuria and urinary frequency, sometimes with fever or a flu-like syndrome, and haematuria, are common, especially with repeated treatment (as in maintenance therapy). Rarely bladder contracture and epididymo-orchitis have been reported. As with vaccination, disseminated BCG infection has occurred rarely and may potentially be fatal. Fever lasting more than 24 hours should be investigated, and antimycobacterial therapy given if necessary. Other reported adverse effects have included hypersensitivity reactions such as rashes and arthralgia, and ocular symptoms including uveitis, conjunctivitis, iritis, and keratitis.

Reviews and studies of the adverse effects of BCG vaccines and their management.[1-6] An increased incidence of local effects has followed intradermal injection of high doses of BCG vaccines.[7,8] The incidence of adverse effects may vary between strains; an increase in incidence was reported in Ireland after withdrawal of a vaccine based on the Evans strain and its replacement with a vaccine containing the SSI strain of BCG.[9]

1. Lotte A, *et al.* Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bull Int Union Tuberc Lung Dis* 1988; 63: 47–59.
2. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bull WHO* 1990; 68: 93–108.
3. Grange JM. Complications of bacille Calmette-Guérin (BCG) vaccination and immunotherapy and their management. *Commun Dis Public Health* 1998; 1: 84–8.
4. FitzGerald JM. Management of adverse reactions to bacille Calmette-Guerin vaccine. *Clin Infect Dis* 2000; 31 (suppl 3): S75–S76.
5. Turnbull FM, *et al.* National study of adverse reactions after vaccination with bacille Calmette-Guérin. *Clin Infect Dis* 2002; 34: 447–53.
6. Bellet JS, Prose NS. Skin complications of bacillus Calmette-Guérin immunization. *Curr Opin Infect Dis* 2005; 18: 97–100.
7. Miles MM, Shaw RJ. Effect of inadvertent intradermal administration of high dose percutaneous BCG vaccine. *BMJ* 1996; 312: 1014.
8. Pullyel JM, *et al.* Adverse local reactions from accidental BCG overdose in infants. *BMJ* 1996; 313: 528–9.
9. Bolger T, *et al.* Complications associated with the bacille Calmette-Guérin vaccination in Ireland. *Arch Dis Child* 2006; 91: 594–7.

Effects on the bones and joints. The risk of osteitis after BCG vaccination varies from country to country and appears to be linked to the strain of bacillus used.[1]

Osteitis or arthritis has also been reported after intravesicular use of BCG (see below).

1. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bull WHO* 1990; 68: 93–108.

Effects on the eyes. Follicular conjunctivitis occurred after accidental contamination of the eye with BCG vaccine.[1] The conjunctivitis responded to topical corticosteroid therapy, but a course of isoniazid was given as a precautionary measure.

For reference to uveitis after intravesical instillation see below.

1. Pollard AJ, George RH. Ocular contamination with BCG vaccine. *Arch Dis Child* 1994; 70: 71.

Effects on the lymphatic system. Lymphadenitis associated with BCG vaccination has been reviewed.[1] It is the most common adverse effect of BCG vaccination and may develop 2 to 24 weeks after vaccination, with most cases occurring within 6 months. The incidence and severity depend on the dose, vaccine strain, the age at vaccination, and the immunological state of the patient. Suppurative BCG lymphadenitis in the form that develops in 30 to 80% of cases; neonates and immunodeficient patients are associated with an increased risk.

The treatment of BCG lymphadenitis remains controversial. Although antibacterials and antituberculous drugs such as isoniazid and rifampicin have been given, there is little evidence to support their use; the non-suppurative (simple) form regresses spontaneously without treatment while suppurating lymph nodes may be drained by needle aspiration and left to heal.

1. Goraya JS, Virdi VS. Bacille Calmette-Guerin lymphadenitis. *Postgrad Med J* 2002; 78: 327–9.

Intravesicular administration. Intravesicular instillation of BCG can give rise to both localised and systemic adverse effects as a consequence of the immune stimulation required to eradicate cancer cells.[1-3] The most serious effects are due to disseminated infection and include severe sepsis with cardiorespiratory manifestations and a disseminated mycobacterial infection with granulomatous pneumonitis and hepatitis; prompt treatment with antimycobacterials is required.[1,4,5] Fatalities have occurred.[6,7] Other reports include severe haemophagocytic syndromes,[8] uveitis,[9,10] and arthritis and osteitis.[11,12] Epididymo-orchitis has also been reported up to 4 years after intravesicular BCG therapy.[13,14]

Initial findings of a study[15] involving 115 patients indicated that prophylactic use of ofloxacin, a fluoroquinolone with tuberculostatic activity, decreased the incidence of moderate to severe adverse effects associated with intravesical BCG without any significant decrease in recurrence-free survival at 12 months. Ofloxacin was given orally after each BCG instillation; a dose of 200 mg was given 6 hours after the first urination with a second dose about 10 to 12 hours later. Long-term study, however, was still needed to confirm these results.

1. Lamm DL. Efficacy and safety of bacille Calmette-Guérin immunotherapy in superficial bladder cancer. *Clin Infect Dis* 2000; 31: S86–S90.
2. Rischmann P, *et al.* BCG intravesical instillations: recommendations for side-effects management. *Eur Urol* 2000; 37 (suppl 1): 33–6.
3. Huang TC. Management of complications of bacillus Calmette-Guerin immunotherapy in the treatment of bladder cancer. *Ann Pharmacother* 2000; 34: 529–32.
4. Mooren FC, *et al.* Systemic granulomatous disease after intravesical BCG insillation. *BMJ* 2000; 320: 219.
5. Gómez-Ferrer Lozano A, *et al.* Neumonitis granulomatosa por instilación endovesical de BCG. *Actas Urol Esp* 2006; 30: 839–42.
6. Peyrère H, *et al.* Fatal systemic reaction after multiple doses of intravesical bacillus Calmette-Guérin for polyposis. *Ann Pharmacother* 2000; 34: 1279–82.
7. Kamphuis JT, *et al.* BCG immunotherapy: be cautious of granulomas. Disseminated BCG infection and mycotic aneurysm as late complications of intravesical BCG instillations. *Neth J Med* 2001; 58: 71–5.
8. Schleinitz N, *et al.* Severe hemophagocytic syndrome after intravesical BCG instillation. *Am J Med* 2002; 112: 593–4.
9. Wertheim M, Astbury N. Bilateral uveitis after intravesical BCG immunotherapy for bladder carcinoma. *Br J Ophthalmol* 2002; 86: 706.
10. Jacob M, *et al.* Pan-uvéite dans les suites d'instillations intravésicales de BCG (Bacille de Calmette et Guérin). *J Fr Ophtalmol* 2006; 29: 552–5.
11. Morgan MB, Iseman MD. Mycobacterium bovis vertebral osteomyelitis as a complication of intravesical administration of Bacille Calmette-Guérin. *Am J Med* 1996; 100: 372–3.
12. Tinazzi E, *et al.* Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. *Rheumatol Int* 2006; 26: 481–8.
13. Menke JJ, Heins JR. Epididymo-orchitis following intravesical bacillus Calmette-Guérin therapy. *Ann Pharmacother* 2000; 34: 479–82.
14. Falkensammer C, *et al.* Late occurrence of bilateral tuberculous-like epididymo-orchitis after intravesical bacille Calmette-Guérin therapy for superficial bladder carcinoma. *Urology* 2005; 65: 175.
15. Colombel M, *et al.* The effect of ofloxacin on bacillus Calmette-Guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. *J Urol (Baltimore)* 2006; 176: 935–9.

Precautions

As for vaccines in general, p. 2375.2.

BCG vaccines may be given with other live vaccines, but if they are not given at the same time it is preferable to allow an interval of 4 weeks between each although the period may be reduced to 10 days if absolutely necessary. However, routine primary immunisation in infants, including the use of live poliomyelitis vaccine, need not be delayed. No further vaccination should be given in the arm used for BCG vaccination for at least 3 months because of the risk of lymphadenitis. BCG vaccination should be postponed in patients with fever or generalised skin infection. In patients with eczema, BCG vaccines should be given at a site free from lesions. Because of the possible risk of disseminated infections, BCG vaccines should not be given to immunocompromised patients including those with HIV infection. Infants born to HIV-positive mothers may be vaccinated once HIV infection has been ruled out; vaccination should be considered in infants of unknown status in areas of high tuberculosis prevalence if there are no signs suggestive of HIV infection. Vaccination is contra-indicated in patients taking antimycobacterial therapy, and those with a history of tuberculosis or a positive tuberculin skin test. Neonates in household contact with a known or suspected case of active tuberculosis should not be vaccinated.

The instillation of *intravesical* BCG should be postponed for 7 to 14 days after any trauma to the urinary tract including transurethral resection, biopsy, and trauma caused by catheterisation. Treatment should also be postponed in patients with acute febrile illness, urinary-tract infection, or gross haematuria. Use is contra-indicated in patients with active tuberculosis, a history of systemic reaction to BCG, or treatment with antimycobacterial therapy. As with vaccination, intravesical BCG should be avoided in immunocompromised patients, including those with HIV infection. Because BCG contains live mycobacteria that may be excreted in the urine, patients should be advised on the risk of contamination, and on appropriate infection control procedures to protect family and close contacts.

Immunocompromised patients. Like other live vaccines, BCG vaccine should not be given to immunocompromised patients including those with symptomatic HIV infections and AIDS. An increased risk of disseminated BCG infection has been seen in infants and children with asymptomatic HIV infections,[1-3] leading to high mortality rates of about 80%. WHO Global Advisory Committee on Vaccine Safety therefore no longer recommends BCG vaccination of infants and children with known HIV infection (see Tuberculosis, HIV-infected Patients, p. 2379.2).

1. Hesseling AC, *et al.* Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clin Infect Dis* 2006; 42: 548–58.
2. Hesseling AC, *et al.* The risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children. *Vaccine* 2007; 25: 14–18.
3. Azzopardi P, *et al.* Bacille Calmette-Guérin vaccine-related disease in HIV-infected children: a systematic review. *Int J Tuberc Lung Dis* 2009; 13: 1331–44.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies BCG vaccine 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 26/10/11)

Interactions

As for vaccines in general, p. 2375.3.

Theophylline. For a report of increased theophylline half-life and serum concentrations after BCG vaccination, see under Theophylline Hydrate, p. 1236.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: ImmuCyst; *Austral.*: ImmuCyst; OncoTICE; *Austria*: ImmuCyst; OncoTICE; *Belg.*: ImmuCyst; OncoTICE; *Braz.*: ImmuCyst; Imunoest; *Canad.*: ImmuCyst; OncoTICE; *Chile*: ImmuCyst†; *China*: SI QI Kang (斯奇康); WeiKa (微卡); Wu Ti Lin Si (乌体林斯); *Cz.*: ImmuCyst; *Fin.*: OncoTICE†; *Fr.*: ImmuCyst; *Ger.*: ImmuCyst†; OncoTICE†; *Gr.*: ImmuCyst; OncoTICE; *Hong Kong*: ImmuCyst; *Hung.*: ImmuCyst; *India*: Onco-BCG; OncoTICE; *Irl.*: ImmuCyst; *Israel*: ImmuCyst; OncoTICE; *Ital.*: ImmuCyst; OncoTICE; *Malaysia*: Glutamate BCG; ImmuCyst; *Mex.*: Cultivo BCG; OncoTICE; *Neth.*: OncoTICE; *Norw.*: OncoTICE; *NZ*: ImmuCyst; OncoTICE; *Philipp.*: Glovax; *Pol.*: OncoTICE; Onko BCG; *Port.*: ImmuCyst; OncoTICE; *Rus.*: Imuron-Vac (Имурон-Вак); *Singapore*: ImmuCyst; *Spain*: ImmuCyst†; OncoTICE; Vejicur; *Swed.*: OncoTICE; *Switz.*: ImmuCyst; OncoTICE; *Thai.*: ImmuCyst; *Turk.*: ImmuCyst; OncoTICE; *UK*: ImmuCyst; OncoTICE; *Ukr.*: Onco-BCG (Онко БЦЖ); *USA*: TheraCys; Tice; *Venez.*: OncoTICE.

Pharmacopoeial Preparations
Ph. Eur.: BCG for Immunotherapy; Freeze-dried BCG Vaccine; USP 36: BCG Live; BCG Vaccine.

Botulism Antitoxins

Antitoxinas botulínicas; Antitoxinas del botulismo; Ботулинические Антитоксины.
ATC — J06AA04.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Botulinum Antitoxin; Immunoserum Botulinicum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxins formed by type A, type B, type E, or any mixture of types A, B, and E, of *Clostridium botulinum*. It contains not less than 500 international units of each of type A and type B and not less than 50 units of type E per mL. It should be stored at 2 degrees to 8 degrees and not be allowed to freeze.

The BP 2014 states that Bot/Ser may be used on the label.

The BP 2014 states that when Mixed Botulinum Antitoxin or Botulinum Antitoxin is prescribed or demanded and the types to be present are not stated, Botulinum Antitoxin prepared from types A, B, and E shall be dispensed or supplied.

NOTE. Some antitoxins used in the UK have not conformed to the requirements of the BP 2014 and Ph. Eur. 8 (having a higher phenol content than the pharmacopoeias allow), and thus have been referred to as **botulism antitoxin** rather than botulinum antitoxin.

Uses and Administration

Botulism antitoxins are used in the postexposure prophylaxis and treatment of botulism. Treatment should be given as early as possible in the course of the disease.

Since the type of botulism toxin is seldom known the polyvalent antitoxin is usually given. Sensitivity testing should always be performed before using the antitoxin.

In the UK, equine-derived trivalent antitoxins containing antitoxin types A, B, and E have been used. One type has contained not less than 500 units/mL of each of the 3 antitoxins. For the treatment of botulism, 20 mL of this antitoxin would be diluted to 100 mL with sodium chloride 0.9% and given by slow intravenous infusion over at least 30 minutes; another 10 mL may be given 2 to 4 hours later if necessary, and further doses at 12- to 24-hour intervals if indicated. Persons who have been exposed to the toxin and in whom symptoms have not developed should be given 20 mL intramuscularly as a prophylactic measure.

A second preparation used for treatment of botulism in the UK has contained 750 units/mL of antitoxin type A, 500 units/mL of antitoxin type B, and 50 units/mL of antitoxin type E. Patients would be given 250 mL by slow intravenous infusion, followed by a further 250 mL by continuous drip infusion. A further 250 mL may be given 4 to 6 hours later if necessary according to response. Patients with severe intoxication should be given an intralumbar injection of 20 mL, particularly if intravenous treatment has produced no improvement; this procedure may be repeated at 24-hour intervals if required.

In the USA, a human-derived intravenous botulism immunoglobulin (BIG-IV) is available for the treatment of patients under 1 year of age with infant botulism caused by toxin type A or B. The recommended dose of 1.5 mL/kg (75 mg/kg), given as a single intravenous infusion, provides a protective level of neutralising antibodies for at least 6 months. A heptavalent botulinum antitoxin active against toxin types A, B, C, D, E, F, and G is also available in the USA for the treatment of naturally occurring noninfant botulism.

Botulism. Botulism[1-4] is caused by the exotoxin of *Clostridium botulinum*, a spore-forming, Gram-positive anaerobe which occurs in soil and mud. There are 3 naturally occurring forms of botulism: *food-borne botulism* caused by ingestion of contaminated foodstuffs, *wound botulism* due to the growth of toxin-releasing organisms in the wound, and *intestinal botulism* (including infant botulism and adult intestinal toxaemia) caused by intestinal colonisation and toxin production. Accidental or intentional exposure to botulinum toxin may result in inhalation botulism (from aerosolisation of botulinum toxin) or iatrogenic botulism (from injection of the toxin). Seven types of *C. botulinum* can be distinguished (types A to G), each producing a different exotoxin; human disease is usually caused by types A, B, and E. The toxin is heat labile, but the spores can survive temperatures of up to 120 degrees.

All forms of botulism produce the same clinical syndrome. Symptoms arise as a result of the toxin blocking the release of acetylcholine at the neuromuscular junction and include symmetrical cranial nerve palsies and descending flaccid paralysis, orthostatic hypotension, dry mouth, and dilated pupils. Gastrointestinal symptoms occur with food-borne or intestinal colonisation botulism. Death is usually from respiratory arrest.

Treatment of botulism is with equine-derived antitoxins and intensive respiratory and supportive therapy. Antitoxins should be given as early as possible as only toxins that are not bound to nerve ending are neutralised; however, antitoxins may still be beneficial if treatment is delayed. Some patients may benefit from drugs, such as fampridine or guanidine, aimed at reversing the neuromuscular blockade. Vaccination has been investigated as a preventive measure in persons at high risk, but is problematic since it may preclude therapeutic or cosmetic use of the toxin.

Infant botulism is of increasing importance, especially in the USA where it is reported to be the most common form of botulism, with honey (see p. 2072.2) reputed to be the most frequent source of infection. In contrast to food-borne botulism, in infant botulism low doses of toxin continue to be released into the gut for some time. Treatment is with intensive supportive care; equine botulism antitoxin used in adults is not generally used for infant botulism because of its serious adverse effects (including serum sickness and anaphylaxis), its short half-life, and the possibility of lifelong sensitisation to equine proteins.[5] A human-derived intravenous botulism immunoglobulin (BIG-IV) is available in the USA for the treatment of patients under 1 year of age with infant botulism caused by toxin type A or B. Clinical studies[5] reported that treatment with BIG-IV within 7 days of hospital admission reduced the length of hospital stay and severity of illness in infant botulism type A or B; treatment given within 3 days was more effective than treatment given 4 to 7 days after admission.

1. Robinson RF, Nahata MC. Management of botulism. *Ann Pharmacother* 2003; 37: 127–31.
2. Health Protection Agency. Guidelines for action in the event of a deliberate release: botulism (issued March 2009). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947315628 (accessed 26/08/10)
3. Sobel J. Botulism. *Clin Infect Dis* 2005; 41: 1167–73.
4. Smith LA. Botulism and vaccines for its prevention. *Vaccine* 2009; 27 (suppl 4): D33–D39.
5. Arnon SS, *et al.* Human botulism immune globulin for the treatment of infant botulism. *N Engl J Med* 2006; 354: 462–71.

Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: BabyBIG.

Pharmacopoeial Preparations
Ph. Eur.: Botulinum Antitoxin.

Bovine Colostrum

Calostro bovino.
UNII — S256WJ3OFQ.

Profile

Bovine colostrum has been used similarly to antisera and human immunoglobulin preparations to provide passive immunity against infectious diseases. Hyperimmune bovine colostra have been prepared from cows previously immunised with specific antigens. In particular, these specific hyperimmune bovine colostra have been tried in cryptosporidiosis and in the prevention of rotavirus diarrhoea in infants. They may also have potential for use against *Helicobacter pylori*, *Shigella* spp., and measles.

Reviews.

1. Kelly GS. Bovine colostrums: a review of clinical uses. *Altern Med Rev* 2003; 8: 378–94. Correction. *ibid.* 2004; 9: 69.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: PM Auscolos; Travelan; *India*: Istrum; Kairlact.

Multi-ingredient Preparations. *Austral.*: PM IQShield; *India*: Immunorm; *Indon.*: Bd-GARD; Biostrum; Brainvit; Calostrum; Curbexon; Curmunos; Hepimun Plus; Idesar Plus; Igastrum Plus; Igastrum; Imustrum; Intrum Plus; Kolivit; Kuminta; Prokids; Stimox; Truvit; Vicotrum; Vistrum; Vitaplex; *Ital.*: Colostrum.

Brucellosis Vaccines

Vacunas de la brucelosis.
ATC — J07AD01.

Profile

A brucellosis vaccine prepared from an antigenic extract of *Brucella abortus* has been used for active immunisation against brucellosis (p. 176.1) in persons at high risk of contracting the disease.

Campylobacter Jejuni Vaccines

Vacunas contra el Campylobacter jejuni.

Profile

An oral vaccine is under development to provide active immunisation against *Campylobacter jejuni* infection.

Cholera Vaccines

Vacunas del cólera.

ATC — J07AE01; J07AE02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Cholera Vaccine; Vaccinum Cholerae). A sterile homogeneous suspension of a suitable killed strain or strains of *Vibrio cholerae*. It consists of a mixture of equal parts of vaccines prepared from smooth strains of 2 main serological types, Inaba and Ogawa of the classical biotype with or without the El Tor biotype. A single strain or several strains of each type may be included. All strains must contain, in addition to their type O antigens, the heat-stable O antigen common to the Inaba and Ogawa types. If more than one strain each of Inaba and Ogawa are used they may be selected to contain other O antigens. It contains not less than 8000 million *V. cholerae* per dose, which does not exceed 1 mL. It contains not more than 0.5% of phenol. It should be stored at 2 degrees to 8 degrees and protected from light.

The BP 2014 states that Cholera may be used on the label.

Ph. Eur. 8: (Cholera Vaccine, Freeze-dried; Vaccinum Cholerae Cryodesiccatum). Cholera vaccine that is freeze-dried and reconstituted immediately before use by the addition of a suitable sterile liquid. Phenol may not be used in the preparation of the dried vaccine. It should be stored at 2 degrees to 8 degrees and be protected from light.

Ph. Eur. 8: (Cholera Vaccine (Inactivated, Oral); Vaccinum Cholerae Perorale Inactivatum). A homogeneous suspension of inactivated suitable strains of *Vibrio cholerae* serogroup O1, representing serotypes and biotypes of epidemic strains. The vaccine may contain the B subunit of cholera toxin (CTB). Just before ingestion, one dose of vaccine suspension is mixed with a suitable buffer as stated on the label. Store at 2 degrees to 8 degrees. Protect from light.

The BP 2014 states that Dried/Cholera may be used on the label.

Uses and Administration

Injectable inactivated whole-cell cholera vaccines have been used for active immunisation against cholera (p. 184.2) but are not considered to be very effective and the immunity conferred is short-lived. They have no role in the management of contacts of cases or in controlling the spread of infection.

Oral vaccines containing either live attenuated or inactivated strains are available in some countries and appear to be more effective than parenteral vaccines (see below). In the UK, an oral vaccine containing inactivated strains of *Vibrio cholerae* O1 and recombinant cholera toxin B subunit is available for use in adults and children aged over 2 years who are travelling to areas of risk. The vaccine is given as a suspension, in doses of 3 mL, mixed with sodium hydrogen carbonate solution. Adults and children aged over 6 years are given two doses, and children aged 2 to 6 years three doses, in each case at weekly intervals. Immunisation should be complete at least 1 week before potential exposure. Booster doses may be given after 2 years in adults and children over 6 years, or after 6 months in children aged 2 to 6 years, if continuous protection is required. Oral vaccines containing a live attenuated form of the *V. cholerae* strain CVD 103-HgR are available in some countries. They are effective against the O1 serogroup of cholera, but do not afford protection against the O139 serogroup. They may be given to adults and children aged over 2 years who are travelling to areas of risk and are given as a single-dose suspension in sodium hydrogen carbonate solution. Immunisation should be carried out at least 1 week before potential exposure. When necessary revaccination is recommended every 6 months.

The WHO International Health Regulations do not require cholera vaccination for travellers as the introduction of cholera into any country cannot be prevented by cholera vaccination. However, travellers may still be asked for evidence of immunisation at some borders.

References.

1. WHO. Cholera vaccines: WHO position paper. *Wkly Epidem Rec* 2010; 85: 117–28. Also available at: http://www.who.int/wer/2010/wer8513.pdf (accessed 22/06/10)

Oral cholera vaccines. Since parenteral cholera vaccines are not considered to be very effective, providing at best 50% protection and confer immunity lasting only 3 to 6 months, attention has turned towards oral vaccines that stimulate intestinal immunity.[1] Both killed and live attenuated oral vaccines have been developed, and both types have been shown to be non-toxic and immunogenic.

Killed vaccines contain inactivated whole *Vibrio cholerae* O1 either alone or with B subunit component of cholera toxin. These vaccines typically produce a protective efficacy of about 60 to 70% and both modify established infections and prevent new ones. Although the vaccines are effective in areas where the El Tor biotype predominates, they are more effective against classical strains. Immunity particularly against El Tor may be less sustained in children under 5 years of age than in older children and adults. The main drawback is the need to give two or more doses at 1- to 2-week intervals to achieve a protective effect. The protective effect is rapidly established but diminishes over time and booster doses are necessary to maintain a high level of immunity.

A live attenuated vaccine is now available containing CVD 103-HgR in which the genes encoding the toxic A subunit are deleted by recombinant techniques.[2,3] This vaccine is effective 8 days after a single dose but less so against El Tor than against classical strains. It is not effective against *V. cholorae* O139.

Live oral vaccines effective against El Tor are now being developed,[4,5] and promising responses have also been reported with a live attenuated O139 vaccine.[6] A number of other candidate vaccines including some potentially more suitable for developing countries, are under development.[7]

The efficacy and cost-effectiveness of oral vaccines to control cholera outbreaks in refugee populations is uncertain.

1. Ryan ET, Calderwood SB. Cholera vaccines. *Clin Infect Dis* 2000; 31: 561–5.
2. Tacket CO, *et al.* Randomized, double-blind, placebo-controlled, multicentered trial of the efficacy of a single dose of live oral cholera vaccine CVD 103-HgR in preventing cholera following challenge with Vibrio cholerae O1 El tor inaba three months after vaccination. *Infect Immun* 1999; 67: 6341–5.
3. Richie E, *et al.* Efficacy trial of single-dose live oral cholera vaccine CVD 103-HgR in North Jakarta, Indonesia, a cholera-endemic area. *Vaccine* 2000; 18: 2399–2410.
4. Tacket CO, *et al.* Volunteer studies investigating the safety and efficacy of live El Tor Vibrio cholerae O1 vaccine strain CVD 111. *Am J Trop Med Hyg* 1997; 56: 533–7.
5. Sack DA, *et al.* Evaluation of Peru-15, a new live oral vaccine for cholera, in volunteers. *J Infect Dis* 1997; 176: 201–5.
6. Coster TS, *et al.* Safety, immunogenicity, and efficacy of live attenuated Vibrio cholerae O139 vaccine prototype. *Lancet* 1995; 345: 949–52.
7. Lopez AL, *et al.* Cholera vaccines for the developing world. *Hum Vaccin* 2008; 4: 165–9.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Slight swelling, erythema, and tenderness occasionally occur at the injection site. Fever and malaise have been reported and general reactions, including anaphylaxis and hypersensitivity reactions, have occurred. Neurological and psychiatric reactions have occasionally occurred.

Gastrointestinal disturbances, headache, dizziness, and respiratory symptoms have followed use of oral cholera vaccine.

Blood group. Patients with blood group O are more likely to experience severe symptoms if infected with cholera of the El Tor or O139 types, and cholera vaccines offer them less protection.[1] It has been suggested that this increased vulnerability should be taken into account in epidemiological planning.

1. Holmner Å, *et al.* Molecular basis of cholera blood-group dependence and implications for a world characterized by climate change. *FEBS Lett* 2010; 584: 2548–55.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies inactivated, whole cell cholera vaccine 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 02/11/11)

Interactions

As for vaccines in general, p. 2375.3.

The oral cholera vaccine available in the UK is acid labile; consequently food should not be consumed for 1 hour before and after use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Orochol; *Austral.*: Dukoral; *Austria*: Dukoral; *Belg.*: Dukoral; *Braz.*: Vacina Oral Contra Colera; *Canad.*: Dukoral; *Chile*: Dukoral; *China*: Oravacs (口服); *Cz.*: Dukoral; *Denm.*: Dukoral; *Fin.*: Dukoral; *Fr.*: Dukoral; *Ger.*: Dukoral; *Hong Kong*: Dukoral; *Hung.*: Dukoral; *Irl.*: Dukoral; *Ital.*: Dukoral; *Malaysia*: Dukoral; *Neth.*: Dukoral; *Norw.*: Dukoral; *NZ*: Dukoral; *Philipp.*: Dukoral; Orochol†; *Pol.*: Dukoral; *Port.*: Dukoral; *S.Afr.*: Dukoral; *Singapore*: Dukoral; *Spain*: Dukoral; *Swed.*: Dukoral; *Switz.*: Dukoral; *Thai.*: Dukoral†; *Turk.*: Dukoral†; *UK*: Dukoral.

Pharmacopoeial Preparations

Ph. Eur.: Cholera Vaccine (Inactivated, Oral); Cholera Vaccine; Freeze-dried Cholera Vaccine.

Contraceptive Vaccines

Vacunas anticonceptivas.

Profile

Various approaches to development of a contraceptive vaccine are under investigation. The molecules being explored target either:

- gamete production (gonadotrophin releasing hormone, follicle-stimulating hormone, and luteinising hormone)
- gamete function (zona pellucida proteins and sperm antigens), or
- gamete outcome (human chorionic gonadotrophin)

Phase I and II clinical studies with human chorionic gonadotrophin vaccines have reported reversible efficacy and lack of immunotoxicity; however, vaccines targeting sperm antigens appear to be the most promising.

Reviews.

1. Delves PJ. The development of contraceptive vaccines. *Expert Opin Invest Drugs* 2002; 11: 1225–37.
2. Aitken RJ. Immunocontraceptive vaccines for human use. *J Reprod Immunol* 2002; 57: 273–87.
3. McLaughlin EA, *et al.* Contraceptive vaccines. *Expert Opin Biol Ther* 2003; 3: 829–41.
4. Ferro VA, Mordini E. Peptide vaccines in immunocontraception. *Curr Opin Mol Ther* 2004; 6: 83–9.
5. Naz RK. Contraceptive vaccines. *Drugs* 2005; 65: 593–603.
6. Naz RK. Status of contraceptive vaccines. *Am J Reprod Immunol* 2009; 61: 11–8.

Crimean-Congo Haemorrhagic Fever Immunoglobulins

Inmunoglobulinas contra la fiebre hemorrágica de Congo-Crimea.

Profile

Preparations containing antibodies against Crimean-Congo haemorrhagic fever have been used for passive immunisation against the disease.

References.

1. Vassilenko SM, *et al.* Specific intravenous immunoglobulin for Crimean-Congo haemorrhagic fever. *Lancet* 1990; 335: 791–2.
2. Ergonul O. Treatment of Crimean-Congo hemorrhagic fever. *Antiviral Res* 2008; 78: 125–31.

Crimean-Congo Haemorrhagic Fever Vaccines

Profile

An inactivated vaccine against Crimean-Congo haemorrhagic fever, derived from *mouse* brains, is used in parts of eastern Europe.

Cytomegalovirus Immunoglobulins

Inmunoglobulinas contra el citomegalovirus.

ATC — J06BB09.

UNII — 129L90A25N (human cytomegalovirus immune globulin).

Description. Cytomegalovirus immunoglobulins containing high levels of specific antibody against CMV have been prepared from human plasma.

Uses and Administration

Cytomegalovirus immunoglobulins are used for passive immunisation against CMV infection. They are used prophylactically, especially in patients undergoing certain transplant procedures. In transplants from CMV-seropositive donors into seronegative recipients, prophylactic use of cytomegalovirus immunoglobulin with ganciclovir should also be considered.

In the USA, a cytomegalovirus immunoglobulin G is available for use in recipients of heart, kidney, liver, lung, and pancreas transplants, and for CMV-seronegative recipients of these organs other than kidney from CMV-seropositive donors. The dosage schedule for kidney transplant recipients is 150 mg/kg by intravenous infusion within 72 hours of transplantation, then 100 mg/kg once every 2 weeks for 4 doses, then 50 mg/kg every 4 weeks for 2 doses. The rate of infusion should start at 15 mg/kg per hour increasing gradually to a maximum rate of 60 mg/kg per hour. For recipients of transplants other than kidney, the recommended dosage schedule is 150 mg/kg within 72 hours of transplantation and then once every 2 weeks for 4 further doses, then 100 mg/kg every 4 weeks for 2 doses. In the UK, cytomegalovirus immunoglobulin is available on a named patient basis for prophylaxis in patients receiving immunosuppressive treatment.

The name sevirumab is applied to a γ-chain human monoclonal cytomegalovirus immunoglobulin G1.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Interactions

As for immunoglobulins in general, p. 2373.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Megalotect; *Austral.*: CMV Immunoglobulin; *Austria*: Cytotect; *Belg.*: Ivegam-CMV; *Canad.*: CytoGam; *Chile*: Cytotect†; *Cz.*: Cytotect; *Ger.*: Cytotect; *Gr.*: Megalotect; *Hong Kong*: Cytotect†; *Hung.*: Cytotect; *Irl.*: Megalotect; *Israel*: Megalotect; *Ital.*: Cytotect; *Neth.*: Megalotect; *Pol.*: Cytotect; *Port.*: Megalotect; *Singapore*: Megalotect; *Switz.*: Cytotect; *Thai.*: Megalotect†; *Turk.*: CytoGam; Cytotect; *Ukr.*: Cytobiotect (Цитобиотект); *USA*: CytoGam.

Cytomegalovirus Vaccines

Vacunas contra el citomegalovirus.

Profile

Several vaccines for active immunisation against CMV infection are under investigation, including some produced by recombinant technology. A live attenuated cytomegalovirus vaccine containing human CMV Towne strain has been investigated in humans since the late 1970s, particularly for the prevention of CMV infection in renal transplant recipients. However, there have been doubts over its safety.

Several promising candidate vaccines against human CMV infection have been developed; a 2004 review noted that 5 had been or were being tested in humans.[1] Attenuated CMV (Towne strain) vaccine was found to be erratic in efficacy and lost segments of its genetic material; to overcome this a second, more robust, vaccine was designed consisting of a chimera between the attenuated CMV and wild-type virus. The third vaccine developed, known as ALVAC, consisted of a canarypox vector with either a glycoprotein B envelope or a core antigen from CMV pp65, a protein found to be recognised by CD8+ T lymphocytes during naturally acquired infection. Fourthly, a protein subunit vaccine consisting of a recombinant envelope glycoprotein had been found to be safe and to induce a neutralising antibody response. The fifth vaccine developed was a mixture of synthetic peptides incorporating a T helper epitope known as CD8+ cytotoxic T cell epitope and a lipid tail. At that time the attenuated cytomegalovirus vaccine, the protein subunit vaccine, and the recombinant vector vaccine had been or were being tested in CMV-negative subjects, and the chimeric vaccine had been tested in CMV-positive patients as a precursor to testing in CMV-negative persons.[1] Further vaccine candidates that had been proposed included DNA vaccines and a vaccine based on recombinant technology.[1] Further development has continued,[2,3] but no candidate has yet come into general use. Some commentators[4] have suggested that reduction or prevention of cytomegalovirus disease may be a more realistic goal for a vaccine than prevention of infection.

1. Arvin AM, *et al.* Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. *Clin Infect Dis* 2004; 39: 233–9.
2. Schleiss MR. Cytomegalovirus vaccine development. *Curr Top Microbiol Immunol* 2008; 325: 361–82.
3. Herr W, Plachter B. Cytomegalovirus and varicella-zoster virus vaccines in hematopoietic stem cell transplantation. *Expert Rev Vaccines* 2009; 8: 999–1021.
4. Khanna R, Diamond DJ. Human cytomegalovirus vaccine: time to look for alternative options. *Trends Mol Med* 2006; 12: 26–33.

Dengue Fever Vaccines

Vacunas del dengue.

Profile

Live attenuated vaccines under study for active immunisation against dengue fever contain dengue virus types 1, 2, 3, and 4 alone or in various combinations. WHO considers that protection against only one or two dengue viruses might actually increase the risk of more serious disease. The ultimate aim is to produce a vaccine active against all types of dengue virus.

Recombinant vaccines are also under investigation.

References.
1. Velzing J, *et al.* Induction of protective immunity against dengue virus type 2: comparison of candidate live attenuated and recombinant vaccines. *Vaccine* 1999; 17: 1312–30.
2. Kanesa-Thasan N, *et al.* Safety and immunogenicity of attenuated dengue virus vaccines (Aventis Pasteur) in human volunteers. *Vaccine* 2001; 19: 3179–88.
3. Rothman AL, *et al.* Induction of T lymphocyte responses to dengue virus by a candidate tetravalent live attenuated dengue virus vaccine. *Vaccine* 2001; 19: 4694–99.
4. Sabchareon A, *et al.* Safety and immunogenicity of tetravalent live-attenuated dengue vaccines in Thai adult volunteers: role of serotype concentration, ratio, and multiple doses. *Am J Trop Med Hyg* 2002; 66: 264–72.
5. Sun W, *et al.* Vaccination of human volunteers with monovalent and tetravalent live-attenuated dengue vaccine candidates. *Am J Trop Med Hyg* 2003; 69 (suppl 6): 24–31.
6. Sabchareon A, *et al.* Safety and immunogenicity of a three dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children. *Pediatr Infect Dis J* 2004; 23: 99–109.
7. Monath TP. Dengue and yellow fever—challenges for the development and use of vaccines. *N Engl J Med* 2007; 357: 2222–5.
8. Edelman R. Dengue vaccines approach the finish line. *Clin Infect Dis* 2007; 45 (suppl 1): S56–60.
9. Hatch S, *et al.* Dengue vaccine: opportunities and challenges. *IDrugs* 2008; 11: 42–5.
10. Webster DP, *et al.* Progress towards a dengue vaccine. *Lancet Infect Dis* 2009; 9: 678–87.
11. Durbin AP, Whitehead SS. Dengue vaccine candidates in development. *Curr Top Microbiol Immunol* 2010; 338: 129–43.
12. Miller N. Recent progress in dengue vaccine research and development. *Curr Opin Mol Ther* 2010; 12: 31–8.

Dental Caries Vaccines

Vacunas de la caries dental.

Profile

Dental caries vaccines consisting of purified proteins from *Streptococcus mutans* or *Str. sobrinus* are under investigation. Monoclonal antibodies are also being studied for local passive immunisation.

Several *animal* studies of candidate vaccines for the prevention of dental caries have shown that immunisation with protein antigens from *Streptococcus mutans* or *Str. sobrinus* can induce salivary IgA antibodies which inhibit both sucrose-dependent or sucrose-independent accumulation of these organisms on tooth surfaces. It is thought that candidate vaccines for study in humans could be given by mucosal application since children are already naturally exposed to the antigens involved during the first years of life. Infection with *Str. mutans* normally occurs from the age of about 18 months and the intention is therefore to vaccinate 1-year-old children in order to intercept colonisation. However, progress towards a vaccine for active immunisation against dental caries requires further clinical evaluation. Passive administration of salivary antibodies to *Str. mutans* has also provided some protection in preclinical studies and small scale studies in humans.[1-4]

1. Koga T, *et al.* Immunization against dental caries. *Vaccine* 2002; 20: 2027–44.
2. Smith DJ. Caries vaccines for the twenty-first century. *J Dent Educ* 2003; 67: 1130–9.
3. Russell MW, *et al.* A caries vaccine? The state of the science of immunization against dental caries. *Caries Res* 2004; 38: 230–5.
4. Smith DJ, Mattos-Graner RO. Secretory immunity following mutans streptococcal infection or immunization. *Curr Top Microbiol Immunol* 2008; 319: 131–56.

Diphtheria Antitoxins

Antitoxinas diftéricas.
ATC — J06AA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria Antitoxin; Immunoserum Diphthericum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxin formed by *Corynebacterium diphtheriae*. It has a potency of not less than 1000 international units/mL when obtained from horse serum and not less than 500 international units/mL when obtained from other mammals. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Dip/Ser may be used on the label.

Uses and Administration

Diphtheria antitoxins neutralise the toxin produced by *Corynebacterium diphtheriae* locally at the site of infection and in the circulation.

Diphtheria antitoxin is used for passive immunisation in suspected cases of diphtheria and should be given without waiting for bacteriological confirmation of the infection. An antibacterial is also usually given (see p. 178.3). Diphtheria antitoxin is generally not used for the prophylaxis of diphtheria because of the risk of provoking a hypersensitivity reaction. Contacts of a diphtheria case should be promptly investigated, given antibacterial prophylaxis and active immunisation with a suitable diphtheria-containing vaccine as appropriate (see below), and kept under observation.

A test dose of diluted diphtheria antitoxin should always be given intradermally to exclude hypersensitivity. In the UK, diphtheria antitoxin is given by intravenous infusion for the treatment of diphtheria of mild to moderate severity in the following recommended doses:

- for *nasal* diphtheria, 10 000 to 20 000 units
- for *tonsillar* diphtheria, 15 000 to 25 000 units
- for *pharyngeal* or *laryngeal* diphtheria, 20 000 to 40 000 units

In cases of combined disease, or when diagnosis is delayed, 40 000 to 60 000 units should be given, and, in severe disease, doses up to 100 000 units used. For most cutaneous infections, diphtheria antitoxin is insufficiently absorbed and is therefore not given; however, if the ulcer is sufficiently large (more than 2 cm^2) and especially if it is membranous, then 20 000 to 40 000 units may be given. Higher doses have been used in some countries.

Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria Antitoxin.

Diphtheria Vaccines

Vacunas de la difteria.
ATC — J07AF01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria Vaccine (Adsorbed); Vaccinum Diphtheriae Adsorbatum). A preparation of diphtheria formol toxoid adsorbed on a mineral carrier. The formol toxoid is prepared from the toxin produced by the growth of *Corynebacterium diphtheriae*. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives, particularly those of the phenolic type. It contains not less than 30 international units per dose. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Ph. Eur. 8: (Diphtheria Vaccine (Adsorbed, Reduced Antigen Content); Vaccinum Diphtheriae, Antigenii Minutum, Adsorbatum). It is an adsorbed diphtheria vaccine containing not less than 2 international units per dose.

The BP 2014 states that for a vaccine for use in the UK, the amount of toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents per dose.

Uses and Administration

Diphtheria vaccines are used for active immunisation against diphtheria. The non-adsorbed vaccine has poor immunogenic properties and its effects are enhanced if given as an adsorbed preparation. For primary immunisation combined diphtheria vaccines, usually diphtheria, tetanus, and pertussis vaccines (p. 2383.3) or diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccines (p. 2385.3), are used. A single-component diphtheria vaccine has sometimes been used, for example in the event of contact with an infected patient or a carrier. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Individuals coming into contact with a case of diphtheria or carrier of a toxigenic strain, or those travelling to an endemic or epidemic area should receive a complete primary course or a reinforcing dose according to age and immunisation history; those not previously immunised should receive a primary course of immunisation, and those previously immunised should receive a single reinforcing dose of a diphtheria-containing vaccine. Contacts of a case of diphtheria or carrier of a toxigenic strain should in

addition receive a prophylactic course of a suitable antibacterial (see p. 178.3). Individuals at repeated risk of exposure to infection may be offered booster doses every 10 years.

Schick testing (p. 2611.2) to ascertain immune status is no longer considered necessary before giving diphtheria vaccine to adults provided that a low dose is given; antibody testing is used to check immunity in those regularly exposed to diphtheria.

In some countries, booster doses of a diphtheria and tetanus vaccine are recommended every 10 years (see under Diphtheria and Tetanus Vaccines, below).

Conjugation to diphtheria toxoid has been used to increase the immunogenicity of other vaccines (see Haemophilus Influenzae Vaccines, p. 2387.2).

References.
1. WHO. Diphtheria vaccine: WHO position paper. *Wkly Epidem Rec* 2006; 81: 24–32. Also available at: http://www.who.int/immunization/wer8103Diphtheria_Jan06_position_paper.pdf (accessed 23/06/10)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Local reactions may occur but are generally not severe in young children; the frequency and severity of reactions is reported to be less in children under 2 years of age than in older children and adults. If diphtheria vaccines or vaccines containing a diphtheria component need to be given to children over the age of 10 years or to adults, vaccines with a reduced content of diphtheria toxoid and intended for adults and adolescents should be used. For further details see Uses and Administration, p. 2382.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diphtheria vaccine 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 02/11/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Difterivaccine; *NZ*: Di Anatoxal†.

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria Vaccine (Adsorbed); Diphtheria Vaccine (Adsorbed, Reduced Antigen Content).

Diphtheria and Tetanus Vaccines

Vacunas de la difteria y el tétanos; Vacunas dobles DT; Vacunas DT.

ATC — J07AM51.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria and Tetanus Vaccine (Adsorbed); Vaccinum Diphtheriae et Tetani Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid adsorbed on a mineral carrier. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international units of diphtheria toxoid and not less than 40 international units of tetanus toxoid per dose. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DT/Vac/Ads(Child) may be used on the label.

The BP 2014 gives Adsorbed Diphtheria-Tetanus Prophylactic as an approved synonym.

Ph. Eur. 8: (Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content); Vaccinum Diphtheriae et Tetani, Antigeni-o(-is) Minutum). It is diphtheria and tetanus vaccine (adsorbed) containing not less than 2 units of diphtheria toxoid and not less than 20 units of tetanus toxoid per dose.

The BP 2014 states that for a vaccine for use in the UK, the amount of diphtheria toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents of diphtheria toxoid per dose.

The BP 2014 states that dT may be used on the label.

Uses and Administration

Combined adsorbed diphtheria and tetanus vaccines may be used for active immunisation, although vaccines used for primary immunisation usually combine diphtheria, tetanus, and pertussis, and sometimes also Haemophilus influenzae and poliomyelitis. Diphtheria and tetanus vaccines are used in some countries for reinforcing doses after primary immunisation; in the USA they are given to adults every 10 years. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

The non-adsorbed combined diphtheria and tetanus vaccines have weaker immunogenic properties than adsorbed vaccines and are no longer recommended.

Booster doses. In many countries, booster doses of combined diphtheria and tetanus vaccines are recommended every 10 years, and studies have been conducted to assess whether this is necessary. Since the incidence of clinical diphtheria in many countries in western Europe and North America approaches zero, it had been considered that there was no need for booster doses in adults, despite low antibody titres, so long as the policy of immunisation during infancy was maintained.[1,2] However, after a report[3] of an outbreak of clinical diphtheria in Sweden after a period of many years during which no indigenous cases of diphtheria had occurred and the disease was regarded as being eliminated from the country, the question of immunity in adults and the need for revaccination again arose. In the USA, it was considered[4] that re-immunisation every 10 years with a diphtheria and tetanus combined vaccine was mandatory and that this combined vaccine should be used whenever a tetanus vaccine was indicated as in treating emergency wounds. Outbreaks of diphtheria in Russia and neighbouring countries[5] have prompted recommendations for booster doses in travellers to these countries.

1. Mathias RG, Schechter MT. Booster immunisation for diphtheria and tetanus: no evidence of need in adults. *Lancet* 1985; i: 1089–91.
2. Anonymous. Diphtheria and tetanus boosters. *Lancet* 1985; i: 1081–2.
3. Rappuoli R, *et al.* Molecular epidemiology of the 1984–1986 outbreak of diphtheria in Sweden. *N Engl J Med* 1988; 318: 12–14.
4. Karzon DT, Edwards KM. Diphtheria outbreaks in immunized populations. *N Engl J Med* 1988; 318: 41–3.
5. Anonymous. Diphtheria immunisation—advice from the Chief Medical Officer. *Commun Dis Rep* 1993; 3: 27.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1. See also under Diphtheria Vaccines, above, and Tetanus Vaccines, p. 2421.2. Diphtheria and tetanus vaccines are reported to produce fewer adverse effects than diphtheria, tetanus, and pertussis vaccines (see under Incidence of Adverse Effects, p. 2384.1).

Dose-related effects. A high incidence of adverse effects was reported in teenagers inadvertently given a high-dose diphtheria and tetanus vaccine intended for use in infants.[1] Most reactions were classified as mild or moderately severe, but severe local or systemic reactions occurred in a third of those reporting reactions.

1. Sidebotham PD, Lenton SW. Incidence of adverse reactions after administration of high dose diphtheria with tetanus vaccine to school leavers: retrospective questionnaire study. *BMJ* 1996; 313: 533–4.

Effects on the nervous system. Encephalopathy is more common after vaccination with diphtheria, tetanus, and pertussis vaccine (p. 2384.1) than with diphtheria and tetanus vaccine. Several cases of encephalopathy occurred in a small region in Italy in children after immunisation against diphtheria and tetanus,[1] although it was not possible to infer a causal relationship. A case of polyradiculoneuritis has been reported in a patient after the use of a diphtheria-tetanus vaccine and was considered most likely to have been due to the tetanus component.[2]

1. Greco D. Case-control study on encephalopathy associated with diphtheria-tetanus immunization in Campania, Italy. *Bull WHO* 1985; 63: 919–25.
2. Holliday PL, Bauer RB. Polyradiculoneuritis secondary to immunization with tetanus and diphtheria toxoids. *Arch Neurol* 1983; 40: 56–7.

GUILLAIN-BARRÉ SYNDROME. Evidence mainly from case reports and uncontrolled studies favoured a causal relationship between vaccination with diphtheria and tetanus vaccines or single-antigen tetanus vaccines and Guillain-Barré syndrome. The data came primarily from immunocompromised patients.[1] However, a later analysis of active surveillance epidemiological studies of Guillain-Barré syndrome and tetanus vaccination history concluded that if an association exists, it must be extremely rare and not of public health significance.[2]

1. Stratton KR, *et al.* Adverse events associated with childhood vaccines other than pertussis and rubella: summary of a report from the Institute of Medicine. *JAMA* 1994; 271: 1602–5.
2. Tuttle J, *et al.* The risk of Guillain-Barré syndrome after tetanus-toxoid-containing vaccines in adults and children in the United States. *Am J Public Health* 1997; 87: 2045–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined diphtheria and tetanus vaccine 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

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Imovax DT; Vacuna Doble; *Austral.*: ADT; CDT†; *Austria*: DiTe Anatoxal†; DT-reduc; Td-pur; *Belg.*: Tedivax; *Braz.*: Dif-Tet-All†; *Canad.*: Td Adsorbed; *Chile*: Imovax DT; *Denm.*: DiTe Booster; *Fin.*: DiTe Booster; *Ger.*: Td-Impfstoff; Td-pur; Td-Rix; *Gr.*: Anatoxal Di Te Berna; DT Vax; *Hong Kong*: Diftet; Imovax DT†; *India*: DT-Vac†; Dual Antigen; *Irl.*: Diftavax†; *Israel*: Imovax DT; *Ital.*: Dif-Tet-All; Diftavax; Ditanrix; *Malaysia*: Adsorbed DT Vaccine; *Norw.*: DiTe Booster; *NZ*: ADT; CDT; DiTe Anatoxal†; *Philipp.*: Di Te Anatoxal†; Td-pur; *Pol.*: DT; *Port.*: Ditanrix; DiTe Booster; DT Vax; *S.Afr.*: DT Vax†; *Singapore*: ADT; CDT; *Spain*: Anatoxal Te Di†; Diftavax; Ditanrix; DiTe Booster; *Swed.*: DiTe Booster; *Switz.*: Ditanrix†; Td-pur; *Thai.*: Adsorbed DT Vaccine; Td-pur; *Turk.*: Di Te Anatoxal; *USA*: Decavac.

Multi-ingredient Preparations. *Irl.*: DiTe Booster.

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria and Tetanus Vaccine (Adsorbed); Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content).

Diphtheria, Tetanus, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos y Haemophilus influenzae.

Profile

Combined adsorbed diphtheria, tetanus, and *Haemophilus influenzae* type b vaccines have been used in some countries for active immunisation of infants. For discussion of immunisation schedules see under Vaccines, p. 2373.3. For concern over the antigenicity of *Haemophilus influenzae* type b vaccine in combined vaccines, see under Haemophilus Influenzae Vaccines, Interactions, p. 2387.3.

Diphtheria, Tetanus, and Hepatitis B Vaccines

ATC — J07CA07.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Hepatitidis B (ADNr) Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, hepatitis B surface antigen, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Profile

Combined diphtheria, tetanus, and hepatitis B vaccines have been used in some countries for active immunisation.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria, Tetanus and Hepatitis B (rDNA) Vaccine (Adsorbed).

Diphtheria, Tetanus, and Pertussis Vaccines

DTP Vaccines; Vacunas de la difteria, el tétanos y la tos ferina.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus and Pertussis (Whole Cell) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis ex Cellulis Integris Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid on a mineral carrier to which a suspension of killed *Bordetella pertussis* has been added. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international

units of diphtheria toxoid, not less than 40 international units if the test is performed in *guinea-pigs*, or 60 international units if the test is performed in *mice*, of tetanus toxoid, and not less than 4 international units of the pertussis component per dose. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTwP may be used on the label.

Ph. Eur. 8: (Diphtheria, Tetanus and Pertussis (Acellular, Component) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis Sine Cellulis ex Elementis Praeparatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTaP may be used on the label.

Uses and Administration

Combined diphtheria, tetanus, and pertussis vaccines are used for active immunisation of children. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Combined adsorbed vaccines may be given by deep subcutaneous or intramuscular injection (vaccines with acellular pertussis components are for intramuscular injection only) in usual doses of 0.5 mL. In the USA, a vaccine with an acellular pertussis component (DTaP) is used as part of the recommended schedule for primary immunisation. Three doses are given at intervals of 2 months (the first preferably at 2 months of age), a fourth dose at least 6 months after the third, and a fifth dose at 4 to 6 years. Specially formulated tetanus toxoid, reduced diptheria toxoid, and acellular pertussis (Tdap) vaccines are licensed for use in persons aged from 10 or 11 years to 64 years of age; it is given to adolescents at 11 to 12 years of age.

Vaccines containing an acellular pertussis component are now preferred to those containing a whole-cell component (see Vaccine Development, p. 2408.3). The non-adsorbed type of combined diphtheria, tetanus, and pertussis vaccines have weaker immunogenic properties than adsorbed vaccines and are no longer recommended.

Reviews.

1. Pichichero ME, *et al.* An adolescent and adult formulation combined tetanus, diphtheria and five-component pertussis vaccine. *Expert Rev Vaccines* 2006; 5: 175–87.
2. Wilson TR. Update on adolescent immunization: review of pertussis and the efficacy, safety, and clinical use of vaccines that contain tetanus-diphtheria-acellular pertussis. *J Pediatr Health Care* 2006; 20: 229–37.
3. Frampton JE, Keating GM. Reduced-antigen, combined diphtheria, tetanus, and acellular pertussis vaccine (Boostrix): a review of its use as a single-dose booster immunization. *BioDrugs* 2006; 20: 371–89.
4. Murphy TV, *et al.* Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008; 57 (RR-4): 1–51.
5. Plosker GL. Combined, reduced-antigen content tetanus, diphtheria, and acellular pertussis vaccine (Boostrix): a review of its use as a single-dose booster immunization in individuals aged 10-64 years in the US. *BioDrugs* 2009; 23: 253–67.
6. Li WC, *et al.* Boostrix: a reduced-dose acellular pertussis vaccine for use in adolescents and adults. *Expert Rev Vaccines* 2009; 8: 1317–27.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1. See also under Diphtheria Vaccines, p. 2383.1, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

The incidence of local reactions and fever is reported to be lower with accelerated immunisation schedules than with former schedules that spread primary immunisation over 6 months. Local reactions and pyrexia occur less commonly after acellular pertussis vaccines than whole-cell pertussis vaccines, especially in children older than 6 months.

In infants with a personal or close family history of seizures, precautions should be taken to avoid pyrexia. See under Pertussis Vaccines for further details of precautions and contra-indications in individuals with a history of neurological problems.

Incidence of adverse effects. The incidence of local reactions is lower with diphtheria and tetanus vaccines combined with an acellular pertussis component (DTaP) than with a whole-cell pertussis component, and is similar to that after diphtheria and tetanus (DT) vaccines. Such reactions are generally mild and self-limiting. Rarely, high fever, persistent or inconsolable crying (possibly as a reaction to pain), hypotonic-hyporesponsive collapse, or short-lived convulsions (frequently febrile convulsions) may occur, and have been reported after both DT and DTaP vaccines with equal frequency. These reactions do not appear to have any long-term consequences. Rare but serious acute neurological complications including encephalopathy and prolonged seizures have been reported after vaccines with a whole-cell pertussis component (see Effects on the Nervous System, p. 2409.1) but the association could be coincidental. Epidemiological studies have shown that such events are exceedingly rare and only occasionally followed by long-term neurological damage. Analysis of these studies has been difficult but authorities in the UK and USA concluded that the evidence was insufficient for a link.

A causal relationship between DTP vaccination and sudden infant death syndrome (SIDS) has not been established and any temporal relationship is likely to be due to chance.[1,2] There is evidence that the risk of SIDS is lower in infants who have been vaccinated.[3]

Immediate anaphylactic reactions have been reported and are regarded as a contra-indication to further use of DTP vaccine. However, the appearance of a rash is not generally regarded as a contra-indication to further doses.

For further details concerning the contra-indications and precautions to be observed for pertussis-containing vaccines, see p. 2409.2.

1. Hoffman HJ, *et al.* Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors. *Pediatrics* 1987; 79: 598–611.
2. Griffin MR, *et al.* Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. *N Engl J Med* 1988; 319: 618–23.
3. Mitchell EA, *et al.* Immunisation and the sudden infant death syndrome. *Arch Dis Child* 1995; 73: 498–501.

Interactions

As for vaccines in general, p. 2375.3.

For a report of a diminished immune response to *Haemophilus influenzae* conjugated vaccine when mixed with diphtheria, tetanus, and acellular pertussis vaccine, see Haemophilus Influenzae Vaccines, p. 2387.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Adacel; Bustrix; Triacel; Vacuna Triple; *Austral.*: Adacel; Boostrix; Infanrix; Tripacel†; *Austria*: Boostrix; *Belg.*: Boostrix; *Braz.*: Vacina Acel Ads Contra Dif, Tet e Coq; Vacina Comb. Contra Dif.-Tet.-Pert. Acel; Vacina Comb. Contra Dift.-Tet.-Coq.Acel; *Canad.*: Adacel; Boostrix; Tripacel; *Chile*: Adacel; *China*: Infanrix (英芬立适); *Cz.*: Adacel; Boostrix; Infanrix; *Denm.*: Di-Te-Ki-Booster; Triaxis; *Fin.*: Boostrix; Di-Te-Kik†; Infanrix†; Triaxis; *Ger.*: Boostrix; Covaxis; Infanrix; *Gr.*: Anatoxal Di Te Per; DT Coq; Infanrix; Triaxis; *Hong Kong*: Boostrix; Diftetkok; Infanrix†; Tripacel†; *Hung.*: Boostrix; *India*: Infanrix; Triple Antigen; Tripvac; *Indon.*: Infanrix; Tripacel; *Irl.*: Infanrix; Triaxis; *Israel*: Acelluvax DTP; Adacel Polio; Adacel; Boostrix; Infanrix; Tripacel; *Ital.*: Boostrix; Infanrix; *Malaysia*: Adacel; Boostrix†; DTP Vaccine; Infanrix; *Mex.*: Boostrix; *Neth.*: Boostrix; Infanrix†; Triaxis; *Norw.*: Boostrix; *NZ*: Adacel; Boostrix; DiTePer Anatoxal†; Infanrix; Tripacel†; Triple Antigen; *Philipp.*: Adacel; Boostrix; DPT, DT COQ; Infanrix; Tripacel†; Tripavac; *Pol.*: Boostrix; DT Coq†; DTaP; DTP; Infanrix DTPa; Tripacel; *Port.*: Boostrix; Infanrix; *Rus.*: Infanrix (Инфанрикс); *S.Afr.*: DTP-Merieux†; Infanrix DTPa; *Singapore*: Boostrix; DTP; Infanrix; Tripacel†; *Spain*: Boostrix; Infanrix; Triaxis; *Swed.*: Boostrix; Infanrix; Triaxis; *Switz.*: Boostrix; *Thai.*: Adacel; Boostrix; DTCoq/DTP†; DTP Vaccine; Infanrix; Tripacel†; *Turk.*: Acelluvax DTP†; Di Te Per Anatoxal; Infanrix DTPa†; Tripacel; *UK*: Trivax-AD; *Ukr.*: Boostrix (Бустрикс); Infanrix (Инфанрикс); *USA*: Adacel; Boostrix; Daptacel; Infanrix; Tripedia.

Multi-ingredient Preparations. *Irl.*: Boostrix.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus and Pertussis (Acellular, Component) Vaccine (Adsorbed); Diphtheria, Tetanus and Pertussis (Whole Cell) Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos, la tos ferina y Haemophilus influenzae.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Haemophili Stirpe b Conjugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product may be presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

Combined adsorbed diphtheria, tetanus, whole-cell or acellular pertussis, and *Haemophilus influenzae* type b vaccines are available in some countries for active immunisation of children. For discussion of immunisation schedules, see under Vaccines, p. 2373.3. Some combined vaccines are not licensed for use in primary immunisation regimens because of concerns over the response to the *Haemophilus influenzae* type b component (see under Interactions of Haemophilus Influenzae Vaccines, p. 2387.3).

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria, Tetanus, and Pertussis Vaccines, above, Haemophilus Influenzae Vaccines, p. 2387.3, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actacel; *Austral.*: Infanrix Hib; *Braz.*: Vacina Comb. Contra Dif.-Tet.-Pert. Acel e HIB; *Chile*: Actacel; Tetract-HIB; *China*: Infanrix + Hib (英芬四联); *Cz.*: Infanrix Hib; Tetract-HIB†; *India*: Easy-4; *Indon.*: Infanrix Hib; Tetract-HIB; *Irl.*: Infanrix Hib; *Israel*: Actacel; Infanrix Hib; Tetract-HIB†; *Malaysia*: Infanrix Hib; *NZ*: Infanrix Hib; *Philipp.*: Infanrix IPV + HIB; Tetract-HIB; *Port.*: Infanrix Hib; *S. Afr.*: Actacel†; Combact-HIB†; *Singapore*: Actacel†; Infanrix Hib; Tetract-HIB†; *Spain*: Infanrix Hib†; *Thai.*: Actacel†; Tetract-HIB†; *Turk.*: Tetract-HIB; *USA*: TriHIBit†; *Venez.*: Vacuna Tetravalente.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component) and Haemophilus Type b Conjugate Vaccine (Adsorbed); Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, Haemophilus Influenzae, and Hepatitis B Vaccines

ATC — J07CA11.

Profile

Combined diphtheria, tetanus, pertussis, *Haemophilus influenzae*, and hepatitis B vaccines are available in some countries for active immunisation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tritanrix HB-HIB; *Chile*: Quinvaxem; *Cz.*: Quintanrix†; *India*: Easy-5; *Mex.*: Tritanrix HB + Hiberix; *Neth.*: Quintanrix†; *Philipp.*: Quinvaxem; *Thai.*: Quinvaxem.

Multi-ingredient Preparations. *NZ*: Tritanrix HB + HIB†.

Diphtheria, Tetanus, Pertussis, and Hepatitis B Vaccines

Vacunas de la difteria, el tétanos, la tos ferina y la hepatitis B.

ATC — J07CA05.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Hepatitidis B (ADNr) Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, hepatitis B surface antigen, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Profile

Combined diphtheria, tetanus, pertussis, and hepatitis B vaccines are available in some countries for active immunisation.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies combined diphtheria, tetanus, pertussis, and hepatitis B vaccine 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)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Infanrix HepB†; *Braz.*: Vacina Comb. Contra Dif.-Tet.-Pert.-Acel e Hepat.B; *China*: Yi Tai (益泰); *Cz.*: Tritanrix HepB; *Gr.*: Infanrix HepB; *India*: Tritanrix HB; *Indon.*: Tritanrix HB†; *Malaysia*: Tritanrix HB; *Mex.*: Tritanrix HB; *Neth.*: Tritanrix-HepB; *NZ*: Infanrix HepB; *Philipp.*: Tritanrix HB; *Port.*: Tritanrix HepB; *S.Afr.*: Tritanrix HB; *Spain*: Tritanrix HB†; *Thai.*: DTP-HB; Tritanrix HB; *Turk.*: Tritanrix HB.

Multi-ingredient Preparations. *India*: Ecovac; *Irl.*: Tritanrix HB.

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component) and Hepatitis B (rDNA) Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis, and Haemophilus Influenzae Vaccines

ATC — J07CA09.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum, Hepatitidis B (ADNr), Poliomyelitidis Inactivatum et Haemophili Stirpe b Coniugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, hepatitis B surface antigen, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product may be presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before or during use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Profile

A combined diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and *Haemophilus influenzae* type b vaccine is available in some countries for active immunisation.

References.
1. Curran MP, Goa KL. DTPa-HBV-IPV/Hib vaccine (Infanrix hexa™). *Drugs* 2003; 63: 673–82.
2. Dhillon S. DTPa-HBV-IPV/Hib Vaccine (Infanrix hexa™): a review of its use as primary and booster vaccination. *Drugs* 2010; 70: 1021–58.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined diphtheria, tetanus, pertussis, heptitis B, poliomyelitis, and haemophilus influenzae vaccine 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)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Infanrix Hexa; *Austral.*: Infanrix Hexa; *Austria*: Infanrix Hexa; *Belg.*: Infanrix Hexa; *Braz.*: Infanrix Hexa†; Vacina Adsorvida Contra Dif, Tet, Coq Acel, Polio Inat Hepat B (Rec) e Hib Conj†; Vacina Comb. Contra Dif.-Tet.-Pert. Acel Hepat.B r-DNA, Polio Inat e HIB; *Canad.*: Infanrix Hexa; *Chile*: Hexavac†; Infanrix Hexa; *Cz.*: Infanrix Hexa; *Fr.*: Infanrixhexa; *Ger.*: Infanrix Hexa; *Gr.*: Hexavac; Infanrix Hexa; *Hong Kong*: Infanrix Hexa; *Hung.*: Hexavac†; *Irl.*: Infanrix Hexa; *Israel*: Infanrix Hexa; *Ital.*: Infanrix Hexa; *Malaysia*: Infanrix Hexa; *Mex.*: Infanrix Hexa; *Neth.*: Infanrix Hexa; *NZ*: Infanrix Hexa; *Philipp.*: Infanrix Hexa; *Pol.*: Infanrix Hexa; *Port.*: Infanrix Hexa; *S.Afr.*: Infanrix Hexa; *Singapore*: Infanrix Hexa; *Spain*: Infanrix Hexa; *Swed.*: Infanrix Hexa; *Switz.*: Infanrix Hexa; *Thai.*: Infanrix Hexa; *Turk.*: Infanrix Hexa; *Ukr.*: Infanrix Hexa (Инфанрикс Гекса); *Venez.*: Infanrix Hexa; Vacuna Conjugada Hexavalente (Hexaca).

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, and Poliomyelitis Vaccines

Vacunas de la difteria, el tétanos, la tos ferina y la poliomielitis.

ATC — J07CA02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Poliomyelitidis Inactivatum Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Whole Cell) and Poliomyelitis (Inactivated) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis ex Cellulis Integris et Poliomyelitidis Inactivatum Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, an inactivated suspension of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTwP/IPV may be used on the label.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigen(s) Content); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Poliomyelitidis Inactivatum, Antigeni-o(-is) Minutum, Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral adsorbent such as aluminium hydroxide or hydrated aluminium phosphate. The amount of diphtheria toxoid per single human dose is reduced compared with vaccines generally used for primary vaccination; the amounts of tetanus toxoid and pertussis components may also be reduced. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that dTaP/IPV may be used on the label.

Uses and Administration

A combined diphtheria, tetanus, pertussis (acellular component), and poliomyelitis (inactivated) vaccine is used for active immunisation. For discussion of immunisation schedules see under Vaccines, p. 2373.3.

In the UK it is used as part of the recommended schedule and is given by intramuscular injection in a single dose of 0.5 mL as a booster at pre-school age (3 years 4 months to 5 years). It is used similarly in the USA. It is not suitable for primary immunisation.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria, Tetanus, and Pertussis Vaccines, p. 2384.1, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined diphtheria, tetanus, pertussis, and poliomyelitis vaccine 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

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tetraxim; *Austral.*: Adacel Polio; Boostrix IPV; Infanrix IPV; Quadracel; *Austria*: Boostrix Polio; Repevax; Tetravac; *Belg.*: Boostrix Polio; Infanrix IPV; Tetravac; *Braz.*: Vacina Acel Ads Contra Dif, Tet e Coq Pol; Vacina Ads Cont Dift, Tet, Coq Acel Polio; *Canad.*: Adacel-Polio; Quadracel; *Cz.*: Adacel Polio; Boostrix Polio; Infanrix Polio; *Denm.*: Di-Te-Ki-Pol; Infanrix Tetra; *Fin.*: Boostrix Polio; Di-Te-Ki-Pol†; Infanrix Polio; Tetravac; *Fr.*: Boostrixtetra; Infanrixtetra; Repevax; Tetravac; *Ger.*: Boostrix Polio; Repevax; *Gr.*: Boostrix Polio; Infanrix Tetra; Repevax; Tetracoq; Tetravac; *Hong Kong*: Adacel Polio; Boostrix Polio; Infanrix IPV; Tetraxim; *Hung.*: Boostrix Polio; Infanrix IPV; Tetraxim; *Irl.*: Boostrix IPV; Infanrix IPV; Tetravac; *Israel*: Boostrix Polio; Infanrix IPV; Tetracoq†; *Ital.*: PolioBoostrix; PolioInfanrix; Tetravac; *Jpn*: Quattrovac; Tetrabik; *Malaysia*: Infanrix IPV; Tetraxim; *Mex.*: Infanrix IPV; *Neth.*: Boostrix Polio; Infanrix IPV; Triaxis Polio; *Norw.*: Boostrix Polio; Repevax; Tetravac; *NZ*: Adacel Polio; Boostrix IPV; Infanrix IPV; Quadracel; *Philipp.*: Tetracoq†; Tetraxim; *Pol.*: Boostrix Polio; DTaP-IPV; *Port.*: Boostrix Polio; Infanrix Tetra; Repevax; Tetravac; *S.Afr.*: Adacel Quadra; Tetraxim†; *Singapore*: Boostrix Polio; *Swed.*: Boostrix Polio; Infanrix Polio; Tetravac; *Switz.*: Boostrix Polio; Infanrix DTPa-IPV; Tetravac; *Thai.*: Adacel Polio; Boostrix Polio; Infanrix IPV; Tetraxim; *Turk.*: Tetracoq; Tetraxim; *UK*: Infanrix IPV; Repevax; *Ukr.*: Infanrix IPV (Инфанрикс ИПВ); *USA*: Kinrix; *Venez.*: Vacuna Adsorbida Tetravalente.

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed); Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigen(s) Content); Diphtheria, Tetanus, Pertussis (Whole Cell) and Poliomyelitis (Inactivated) Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos, la tos ferina, la poliomielitis y Haemophilus influenzae.

ATC — J07CA06.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum Poliomyelitidis Inactivatum et Haemophili Stirpe b Conjugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product is presented either as a pentavalent liquid formulation in the same container, or as a tetravalent liquid formulation with the freeze-dried Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTaP/IPV/Hib may be used on the label.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Whole Cell), Poliomyelitis (Inactivated) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis ex Cellulis Integris, Poliomyelitidis Inactivatum et Haemophili Stirpe b Conjugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, an inactivated suspension of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product is presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTwP/IPV/Hib may be used on the label.

The symbol † denotes a preparation no longer actively marketed

Uses and Administration

A combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* type b vaccine is used for active immunisation of children. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

In the UK it is used as part of the recommended schedule for primary immunisation. It is given by intramuscular injection in usual doses of 0.5 mL; three doses are given at intervals of one month, starting preferably at 2 months of age. Although it is not licensed for use after a child's fourth birthday, the national schedule considers it may be used up to the age of 10 years.

In the USA, it is licensed for use in infants and children from 6 weeks to 4 years of age and may be given as part of the recommended immunisation schedule at ages 2, 4, 6, and 15 to 18 months. It is not indicated for the booster dose at 4 to 6 years of age; however, if it is given accidentally to children 5 years and older, it may be counted as a valid dose.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria, Tetanus, and Pertussis Vaccines, p. 2384.1, Haemophilus Influenzae Vaccines, p. 2387.3, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

Premature neonates. In an observational study[1] of 78 very-low-birth-weight premature neonates given a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine before hospital discharge, increased incidences of apnoea, bradycardia, desaturation, or oxygen requirement occurred in 47% overall within 24 to 48 hours of vaccination. All neonates with increased events returned to baseline within 48 to 72 hours and there was no detrimental impact on clinical course. The authors considered that, although monitoring and appropriate intervention were required, delaying vaccination was not warranted, a view in line with UK and USA official recommendations (see p. 2375.3).

1. Pfister RE, *et al.* Safety of DTaP-based combined immunization in very-low-birth-weight premature infants: frequent but mostly benign cardiorespiratory events. *J Pediatr* 2004; **145**: 58–66.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine 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

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pentaxim; *Austral.*: Pediacel†; Poliacel†; *Braz.*: Poliacel; Vacina Acel Ads Contra Dif, Tet, Coq e Polio Inat Comb C/Vac Conj Contra Hib†; Vacina Comb. Contra Dif.-Tet.-Pert. Acel, Polio Inat e HIB; *Canad.*: Pediacel; Pentacel; *Chile*: Pentact-HIB†; *China*: Pentaxim (潘太欣); *Cz.*: Infanrix IPV + Hib; Pediacel; *Denm.*: Di-Te-Ki-Pol/Act-Hib; *Fin.*: Infanrix Polio + Hib; Pentavac; *Fr.*: Infanrixquinta; Pentavac; *Ger.*: Infanrix IPV + Hib; Pentavac; *Gr.*: Infanrix IPV + Hib; Pentavac; *Hong Kong*: Infanrix IPV + Hib; Pediacel; Pentact-HIB†; Pentaxim; *Hung.*: Infanrix IPV + Hib; Pentaxim; *Indon.*: Pediacel; *Irl.*: Infanrix IPV + Hib; Pediacel; Pentavac; *Israel*: Infanrix Polio IPV - Hib; Pediacel; Pentact-HIB; Poliacel-Act-Hib; *Ital.*: Pentavac; *Malaysia*: Infanrix IPV + Hib; Pediacel; Pentaxim; *Mex.*: Infanrix IPV + Hib; Pediacel; *Neth.*: DKTP-Hib†; Infanrix IPV + Hib; Pediacel; *Norw.*: Infanrix Polio + Hib; *NZ*: Infanrix IPV + Hib; Poliacel†; *Philipp.*: Pentact-HIB†; Pentaxim; *Pol.*: Infanrix IPV + Hib; Pentaxim; *Port.*: Infanrix IPV + Hib; Pediacel; Pentavac; *S.Afr.*: Pentaxim; *Singapore*: Infanrix IPV + Hib; Pediacel; *Spain*: Infanrix IPV + Hib; Pentavac; *Swed.*: Infanrix Polio + Hib; Pentavac; *Switz.*: Infanrix DTPa-IPV+Hib; Pentavac; *Thai.*: Infanrix IPV + Hib; Pediacel; Pentaxim; *Turk.*: Infanrix IPV-HIB†; Pentact-HIB; Pentaxim; Poliacel; *UK*: Infanrix IPV + Hib; Pediacel; *USA*: Pentacel; *Venez.*: Infanrix IPV + Hib; Vacuna Adsorbida Pentavalente.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Whole Cell), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hepatitis B Vaccines

ATC — J07CA12.

Uses and Administration

A combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and hepatitis B vaccine is available in some countries for active immunisation of children.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria, Tetanus, and Pertussis Vaccines, p. 2384.1, Hepatitis B Vaccines, p. 2390.3, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Infanrix Penta; *Cz.*: Infanrix Penta; *Gr.*: Infanrix Penta; *Irl.*: Infanrix Penta; *Ital.*: Infanrix Penta†; *Neth.*: Infanrix Penta; *NZ*: Infanrix Penta; *Pol.*: Infanrix Penta; *Port.*: Infanrix Penta; *USA*: Pediarix.

Diphtheria, Tetanus, and Poliomyelitis Vaccines

Vacunas de la difteria, el tétanos y la poliomielitis.

ATC — J07CA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus and Poliomyelitis (Inactivated) Vaccine (Adsorbed. Reduced Antigens(s) Content); Vaccinum Diphtheriae, Tetani et Poliomyelitidis Inactivatum, Antigeni-o(-is) Minutum, Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, suitable strains of human polioviruses types 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral adsorbent such as aluminium hydroxide or hydrated aluminium phosphate. The amount of diphtheria toxoid per single human dose is reduced compared with vaccines generally used for primary vaccination; the amount of tetanus toxoid may also be reduced. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

A combined diphtheria, tetanus, and poliomyelitis (inactivated) vaccine is used for active immunisation. For discussion of immunisation schedules see under Vaccines, p. 2373.3.

In the UK it is used as part of the recommended schedule and is given by intramuscular injection in a single dose (usually 0.5 mL) as a booster at the ages of 13 to 18 years. It is not licensed for primary immunisation.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria and Tetanus Vaccines, p. 2383.2, and Tetanus Vaccines, p. 2421.2.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Revaxis; *Belg.*: Revaxis; *Canad.*: Td-Polio; *Fr.*: DT Polio†; Revaxis; *Ger.*: Revaxis; Td-Virelon†; *Gr.*: Revaxis; *Hung.*: Dultavax; *Irl.*: Revaxis; *Israel*: Dultavax; *Ital.*: Revaxis; *Neth.*: Revaxis; *Pol.*: Dultavax; *Port.*: Revaxis; *S.Afr.*: Td-Polio†; *Switz.*: Revaxis; Td-Virelon†; *UK*: Revaxis.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus, and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigen(s) Content).

Endotoxin Antibodies

Anticuerpos antiendotoxinas.

Profile

Antibodies against the endotoxin of Gram-negative bacteria have been tried as adjunctive therapy for the treatment and prevention of Gram-negative bacteraemia and shock.

Early preparations consisted of antisera prepared from the sera of donors immunised with *Escherichia coli* J5; these were superseded by human and murine IgM monoclonal antibodies. Nebacumab (HA-1A) is a human monoclonal IgM antibody that binds specifically to the lipid A domain of endotoxin. Lipid A in the circulation releases tumour necrosis factor and other cytokines from macrophages and endothelial cells which may ultimately culminate in physiological effects such as multiple organ failure. Despite early promising results of clinical studies the safety of nebacumab in patients without Gram-negative septicaemia was questioned and the product was withdrawn.

A murine monoclonal IgM antibody (edobacomab; E5) has also undergone clinical studies although results have been disappointing.

Epstein-Barr Virus Vaccines

Vacunas del virus de Epstein-Barr.

Profile

Several Epstein-Barr virus vaccines are under investigation for active immunisation against infectious mononucleosis and post-transplant lymphoproliferative disorders.

Epstein-Barr virus is a herpesvirus that is ubiquitous in the adult population. It only causes clinical illness where primary infection occurs in adolescence or adulthood, when it prompts the symptoms of infectious mononucleosis in about 50% of cases. More than 90% of the world's population, however, carry the virus as a lifelong latent infection of B-lymphocytes and, as a result, Epstein-Barr virus can also be associated with malignancies including lymphoproliferative diseases, Burkitt's lymphoma, gastric carcinoma, oral hairy leucoplakia, nasopharyngeal carcinoma, and Hodgkin's disease.

Vaccines against Epstein-Barr virus infection are under investigation[1-3] and the main focus has been towards the development of a vaccine to prevent primary infection or to minimise its consequences, namely infectious mononucleosis and post-transplant lymphoproliferative disease, rather than towards the malignancies associated with the virus which occur in relatively fewer patients. Two main approaches have been adopted, the first of which seeks to exploit the major envelope glycoprotein of the virus, gp340, because of its ability to induce neutralising antibodies. This vaccine may prevent infectious mononucleosis by moderating the initial viral replication and spread during primary infection, thereby curtailing the cytotoxic T-lymphocyte response to lytic antigens that would otherwise invoke the immunological processes responsible for clinical symptoms. The second approach is based on the induction of cytotoxic T-cells specific to Epstein-Barr virus, thereby aiming to reduce the clinical symptoms of infectious mononucleosis rather than to prevent primary infection.

Potential future vaccines for malignancies associated with Epstein-Barr virus are likely to be therapeutic rather than preventative and to exploit the presence of the virus in tumour cells; alternatively they may be focussed on tumour antigens not encoded by Epstein-Barr virus.[1,2]

1. Moss DJ, *et al.* Candidate vaccines for Epstein-Barr virus. *BMJ* 1998; **317**: 423–4.
2. Macsween KF, Crawford DH. Epstein-Barr virus—recent advances. *Lancet Infect Dis* 2003; **3**: 131–40.
3. Lockey TD, *et al.* Epstein-Barr virus vaccine development: a lytic and latent protein cocktail. *Front Biosci* 2008; **13**: 5916–27.

Escherichia Coli Vaccines

Vacunas de Escherichia coli.

Profile

Vaccines against enterotoxigenic strains of *Escherichia coli* are under investigation. Vaccine candidates include toxoids, inactivated whole bacteria, purified surface antigens, and live oral vaccines.

Infectious diarrhoea remains a major source of morbidity and mortality in the world and a significant proportion is caused by pathogenic strains of *Escherichia coli* While it is considered feasible to develop effective vaccines against *E. coli*, at present there are no such vaccines available. Current approaches against enteropathogenic *E. coli* (EPEC) and enterohaemorrhagic *E. coli* (EHEC) have focussed on three main areas: the EPEC and EHEC proteins involved in colonisation of the intestine, the EHEC O157-specific side-chain of lipopolysaccharides, and the immunogenicity of Shiga toxin produced by the organism. While vaccination against EPEC has to be directed towards susceptible human populations, there are two possible approaches with regard to EHEC, namely vaccination of either humans or the animal reservoir, cattle. Studies of vaccine candidates are ongoing *in vitro*, in *animal* models, and in healthy subjects. For both pathogens, however, the development of vaccines would not in itself serve to eradicate the spread of infections

and would need to be accompanied by public health campaigns to increase food hygiene and monitoring of water supplies and facilities.[1]

Enterotoxigenic *E. coli* (ETEC) is a major cause of travellers' diarrhoea. A phase II placebo-controlled study[2] found that a vaccine containing heat-labile enterotoxin from ETEC given as a skin patch (2 patches applied 2 to 3 weeks apart), reduced the risk of moderate to severe travellers' diarrhoea by 75% and severe diarrhoea by 84%. In vaccinated travellers who got diarrhoea, the illness was significantly shorter and milder.

Further references.[3-8]

1. Horne C, *et al.* Current progress in enteropathogenic and enterohemorrhagic Escherichia coli vaccines. *Expert Rev Vaccines* 2002; 1: 483–93.
2. Prech SA, *et al.* Use of a patch containing heat-labile toxin from Escherichia coli against travellers' diarrhoea: a phase II, randomised, double-blind, placebo-controlled field trial. *Lancet* 2008; 371: 2019–25.
3. Boedeker EC. Vaccines for enterotoxigenic Escherichia coli: current status. *Curr Opin Gastroenterol* 2005; 21: 15–9.
4. Steffen R, *et al.* Vaccination against enterotoxigenic Escherichia coli, a cause of travelers' diarrhea. *J Travel Med* 2005; 12: 102–7.
5. Walker RI, *et al.* Ad Hoc ETEC Technical Expert Committee. Analysis of strategies to successfully vaccinate infants in developing countries against enterotoxigenic E. coli (ETEC) disease. *Vaccine* 2007; 25: 2545–66.
6. Goldwater PN. Treatment and prevention of enterohemorrhagic Escherichia coli infection and hemolytic uremic syndrome. *Expert Rev Anti Infect Ther* 2007; 5: 653–63.
7. Serna A, Boedeker EC. Pathogenesis and treatment of Shiga toxin-producing Escherichia coli infections. *Curr Opin Gastroenterol* 2008; 24: 38–47.
8. Svennerholm AM, Tobias J. Vaccines against enterotoxigenic Escherichia coli. *Expert Rev Vaccines* 2008; 7: 795–804.

Gas-gangrene Antitoxins

Antitoxinas de la gangrena gaseosa.
ATC — J06AA05.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Gas-gangrene Antitoxin (Novyi); Immunoserum Gangraenicum (Clostridium Novyi)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium novyi*. It has a potency of not less than 3750 international units/mL. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Nov/Ser may be used on the label.

The BP 2014 gives Gas-gangrene Antitoxin (Oedematiens) as an approved synonym.

Ph. Eur. 8: (Gas-gangrene Antitoxin (Perfringens); Immunoserum Gangraenicum (Clostridium Perfringens)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium perfringens*. It has a potency of not less than 1500 international units/mL. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Perf/Ser may be used on the label.

Ph. Eur. 8: (Gas-gangrene Antitoxin (Septicum); Immunoserum Gangraenicum (Clostridium Septicum)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium septicum*. It has a potency of not less than 1500 international units/mL. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Sep/Ser may be used on the label.

Ph. Eur. 8: (Gas-gangrene Antitoxin, Mixed; Immunoserum Gangraenicum Mixtum). It is prepared by mixing Gas-gangrene Antitoxin (Novyi), Gas-gangrene Antitoxin (Perfringens), and Gas-gangrene Antitoxin (Septicum) in appropriate quantities. It has a potency of not less than 1000 international units/mL of Gas-gangrene Antitoxin (Novyi), not less than 1000 international units/mL of Gas-gangrene Antitoxin (Perfringens), and not less than 500 international units/mL of Gas-gangrene Antitoxin (Septicum). It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Gas/Ser may be used on the label.

Profile

Gas-gangrene antitoxins have been used for the treatment of gas gangrene and for prophylaxis in patients at risk after injury. They are now seldom used and have been superseded by antibacterials. Monovalent gas-gangrene antitoxins have been little used in practice owing to the difficulty of rapidly identifying the infecting organism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Aggs.

Pharmacopoeial Preparations

Ph. Eur.: Gas-gangrene Antitoxin (Novyi); Gas-gangrene Antitoxin (Perfringens); Gas-gangrene Antitoxin (Septicum); Mixed Gas-gangrene Antitoxin.

Gonococcal Vaccines

Gonorrhoea Vaccines; Vacunas de la gonorrea.

Profile

Experimental gonococcal vaccines, produced usually from the surface antigens of *Neisseria gonorrhoeae*, have been investigated.

Haemophilus Influenzae Vaccines

Vacunas de Haemophilus influenzae.
ATC — J07AG01 (B, purified antig. conjugate).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Haemophilus type b Conjugate Vaccine; Vaccinum Haemophili Stirpe B Conjugatum). A liquid or freeze-dried preparation of a polysaccharide, polyribosylribitol phosphate (PRP), derived from a suitable strain of *Haemophilus influenzae* type b, covalently bound to a carrier protein. The carrier protein, when conjugated to PRP, is capable of inducing a T-cell-dependent B-cell immune response to the polysaccharide. Carrier proteins currently approved are diphtheria toxoid, tetanus toxoid, CRM 197 diphtheria protein, and meningococcal group B outer membrane protein (OMP). It should be stored at 2 degrees to 8 degrees and protected from light.

The BP 2014 states that Hib may be used on the label.

Uses and Administration

Haemophilus influenzae (Hib) vaccines are used for active immunisation against *Haemophilus influenzae* type b infections. Vaccines are prepared from the capsular polysaccharide of *H. influenzae* type b and immunogenicity, especially in young children, is improved by linking the polysaccharide to a protein carrier to form a conjugate vaccine.

Different proprietary vaccines may be conjugated to differing proteins but are generally regarded as interchangeable.

Haemophilus Influenzae Conjugate Vaccine (Diphtheria Toxoid Conjugate) (PRP-D) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to diphtheria toxoid.

Haemophilus Influenzae Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (HbOC) consists of oligosaccharides derived from the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to a non-toxic variant of diphtheria toxin isolated from *Corynebacterium diphtheriae*.

Haemophilus Influenzae Conjugate Vaccine (Meningococcal Protein Conjugate) (PRP-OMP or PRP-OMPC) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to an outer membrane protein complex of *Neisseria meningitidis* group B.

Haemophilus Influenzae Conjugate Vaccine (Tetanus Toxoid Conjugate) (PRP-T) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to tetanus toxoid.

For primary immunisation either combined vaccines or single-component Haemophilus influenzae vaccines may be used.

In the UK, a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine (p. 2385.3) is used. Children over 1 year of age and under 10 years of age who have not been immunised against *Haemophilus influenza* or have not completed a primary vaccination course of diphtheria, tetanus, pertussis, or polio, should be given 3 doses of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine. Those who have completed a primary vaccination course of diphtheria, tetanus, pertussis, and polio, should receive a single dose of a combined *Haemophilus influenzae* and meningococcal C conjugate vaccine. Routine use in children older than 10 years or adults is not recommended in the UK, but asplenic children (over 10 years of age) and adults who have not been previously immunised should receive two doses of combined *Haemophilus influenzae* and meningococcal C conjugate vaccine, two months apart.

In the USA, primary immunisation is also carried out in conjunction with diphtheria, tetanus, and pertussis vaccination. If a meningococcal protein conjugate vaccine is used, only 2 doses are given for the primary course. A reinforcing dose using any of the available vaccines is given at 12 to 15 months of age.

Where compatibility has been shown, Hib vaccines may be mixed immediately before use with diphtheria, tetanus, and pertussis vaccines (but see Interactions, below).

References.

1. WHO. WHO position paper on *Haemophilus influenzae* type b conjugate vaccines. *Wkly Epidem Rec* 2006; 81: 445–52. Also available at: http://www.who.int/immunization/REH_47_8_pages.pdf (accessed 23/06/10)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Erythema multiforme and transient cyanosis of the lower limbs have been reported rarely in children receiving haemophilus influenzae-containing vaccines.

Effects on the nervous system. Guillain-Barré syndrome has been reported[1] after vaccination with haemophilus influenzae conjugate vaccines in a small number of infants. In one report, onset of symptoms occurred within 1 week of vaccination of 3 infants with an haemophilus influenzae conjugate vaccine (diphtheria toxoid conjugate). However, a causal relationship has not yet been established.

1. D'Cruz OP, *et al.* Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) after immunization with Haemophilus influenzae type b conjugate vaccine. *J Pediatr* 1989; 115: 743–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies haemophilus influenzae vaccines 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

As for vaccines in general, p. 2375.3.

Antineoplastics. Haemophilus influenzae infection occurred in a child who had received antineoplastic therapy despite having completed a primary course of immunisation before the neoplasia was diagnosed.[1] A subsequent booster dose produced an adequate antibody response. Antineoplastic therapy may have impaired the T-cell response to infection.

1. Jenkins DR, *et al.* Childhood neoplasia and Haemophilus influenzae type b vaccine failure. *Lancet* 1996; 348: 131.

Diphtheria, tetanus, and pertussis vaccines. Some haemophilus influenzae conjugated vaccines may be mixed with diphtheria, tetanus, and pertussis vaccines before use without adversely affecting the immunogenicity of the components[1,2] although there has also been a report of reduced immunogenicity.[3] Manufacturers may provide further information on compatibility. The safety and efficacy of giving a conjugate haemophilus influenza vaccine with other childhood vaccines has been reviewed.[4,5]

1. Miller MA, *et al.* Safety and immunogenicity of PRP-T combined with DTP: excretion of capsular polysaccharide and antibody response in the immediate post-vaccination period. *Pediatrics* 1995; 95: 522–7.
2. Mulholland EK, *et al.* The use of Haemophilus influenzae type b-tetanus toxoid conjugate vaccine mixed with diphtheria-tetanus-pertussis vaccine in Gambian infants. *Vaccine* 1996; 14: 905–9.
3. Eskola J, *et al.* Randomised trial of the effect of co-administration with acellular pertussis DTP vaccine on immunogenicity of Haemophilus influenzae type b conjugated vaccine. *Lancet* 1996; 348: 1688–92.
4. Knuf M, *et al.* Immunogenicity of routinely used childhood vaccines when coadministered with the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV). *Pediatr Infect Dis J* 2009; 28(4 suppl): S97–S108.
5. Chevallier B, *et al.* Safety and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) when coadministered with routine childhood vaccines. *Pediatr Infect Dis J* 2009; 28(4 suppl): S109–S118.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Hiberix; PedvaxHIB; *Austria*: Act-HIB; *Belg.*: Act-HIB; *Braz.*: PedvaxHIB; Vacina Conj Com Proteina Tetanica HIB; Vacina Conj Contra Haemophilus Influenzae Tipo B; *Canad.*: Act-HIB; PedvaxHIB; *Chile*: Act-HIB; *China*: Act-HIB (安尔宝); He Er Bei (河儿贝); Hiberix (贺新立适); PedvaxHIB (雪泽欣); *Cz.*: Act-HIB†; Hiberix; *Denm.*: Act-HIB; *Fin.*: Act-HIB; Hiberix; *Fr.*: Act-HIB; *Gr.*: Act-HIB; Hiberix; HibTITER; *Hong Kong*: Act-HIB; Hiberix; PedvaxHIB†; *Hung.*: Act-HIB; *India*: Act-HIB; Hiberix; HIBest; HibTITER; Vaxim HIB†; *Indon.*: Act-HIB; Hiberix; PedvaxHIB; *Irl.*: Act-HIB†; Hiberix†; *Israel*: Act-HIB; Hiberix; *Ital.*: Act-HIB; Hiberix; Vaxem Hib; *Malaysia*: Hiberix; *Mex.*: PedvaxHIB; *Neth.*: Act-HIB; Hiberix; *Norw.*: Act-HIB; *NZ*: Act-HIB; Hiberix; *Philipp.*: Act-HIB; Hiberix; Vaxem Hib; *Pol.*: Act-HIB; Hiberix; HibTITER; PedvaxHIB; *Port.*: Act-HIB; Hiberix; *Rus.*: Hiberix (Хиберикс); *S.Afr.*: Act-HIB†; Hiberix; *Singapore*: Act-HIB†; Hiberix; HibTITER; *Spain*: Hiberix; *Swed.*: Act-HIB; *Switz.*: Hiberix; *Thai.*: Act-HIB; Hiberix; PedvaxHIB; Vaxem Hib;

Turk.: Act-HIB; Hiberix; PedvaxHIB; *UK*: Hiberix†; *USA*: Act-HIB; Hiberix; OmniHIB; PedvaxHIB; *Venez.*: Hiberix.

Pharmacopoeial Preparations
Ph. Eur.: Haemophilus Type b Conjugate Vaccine.

Haemophilus Influenzae and Hepatitis B Vaccines

Vacunas de Haemophilus influenzae y la hepatitis B.
ATC — J07CA08.

Uses and Administration

Haemophilus influenzae type b (Hib) conjugate and hepatitis B vaccines are available in some countries for active immunisation as part of the primary immunisation of infants born to HBsAg-negative mothers. In the USA, an *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine is used. It is given in a schedule of 3 doses, 0.5 mL being given intramuscularly at 2 months, 4 months, and 12 to 15 months of age. Use in infants less than 6 weeks old is not recommended.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Comvax; *Cz.*: Procomvax†; *Gr.*: Procomvax; *Irl.*: Procomvax†; *Mex.*: Comvax; *Neth.*: Procomvax†; *NZ*: Comvax; *Pol.*: Procomvax†; *Port.*: Procomvax†; *Singapore*: Comvax; *USA*: Comvax.

Haemophilus Influenzae and Meningococcal Vaccines

Pharmacopoeias. *Br.* includes a monograph.

BP 2014: (Haemophilus Type b and Meningococcal Group C Conjugate Vaccine). It is prepared from purified polysaccharides derived from a suitable strain of *Neisseria meningitidis* group C and from a suitable strain of *Haemophilus influenzae*, type b covalently bound to a carrier protein. A suitable adjuvant, a suitable antimicrobial preservative, and a stabiliser may be added to the bulk conjugates of the components. The product is presented as a combined lyophilisate of the haemophilus type b and meningococcal group C components together with the solvent in a separate container. The final product is prepared by mixing the contents of the two containers immediately before use. The label may state Hib/MenC.

Profile

A combined *Haemophilus influenza* type b and meningococcal C conjugate vaccine is available for active immunisation in some countries; in the UK a single dose may be given to children between 1 and 10 years of age who have completed a primary vaccination course of diphtheria, tetanus, pertussis, and polio. A booster dose of the combination vaccine is recommended at 12 months for children who have received a complete primary course of three *Haemophilus influenza* type b-containing vaccines. Two doses given 2 months apart may be given to asplenic children (over 10 years of age) or adults who have not been previously immunised.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Irl.*: Menitorix; *UK*: Menitorix; *USA*: MenHibrix.

Pharmacopoeial Preparations
BP 2014: Haemophilus Type b and Meningococcal Group C Conjugate Vaccine.

Haemophilus Influenzae and Poliomyelitis Vaccines

ATC — J07CA04.

Profile

Combined haemophilus influenzae type b conjugate and inactivated poliomyelitis vaccines have been used in some countries for active immunisation of infants.

Haemorrhagic Fever with Renal Syndrome Vaccines

HFRS Vaccine; Vaccinum Haemorrhagia Febris cum Renis Sindronum; Vacunas de la fiebre de Korín; Vacunas de la fiebre hemorrágica con síndrome renal; Vacunas de la fiebre hemorrágica de Corea y Extremo Oriente; Vacunas de la fiebre renal epidémica; Vacunas de la nefrosonefritis hemorrágica.

Description. A fluid or freeze-dried preparation of a suitable hantavirus grown in the neural tissue of suckling rodents or in cell cultures and inactivated. The fluid vaccine should be stored at 2 degrees to 8 degrees and not allowed to freeze. The freeze-dried form should be stored below 10 degrees.

Profile

Inactivated viral vaccines against haemorrhagic fever with renal syndrome have been investigated and are available in some countries, but there have been problems producing a sufficient and sustained immune response.

References.

1. Sohn YM, *et al.* Primary humoral immune responses to formalin inactivated hemorrhagic fever with renal syndrome vaccine (Hantavax): consideration of active immunization in South Korea. *Yonsei Med J* 2001; 42: 278–84.
2. Cho HW, *et al.* Review of an inactivated vaccine against hantaviruses. *Intervirology* 2002; 45: 328–33.
3. Park K, *et al.* Protective effectiveness of hantavirus vaccine. *Emerg Infect Dis* 2004; 10: 2218–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: HaBiVa (汉必威); HaPuVa (汉普威); You Er Jian (佑尔健).

Helicobacter Pylori Vaccines

Vacunas de Helicobacter pylori.

Profile

Vaccines against *Helicobacter pylori* are being developed for prophylaxis of peptic ulcer disease and gastric cancer.

Studies in *animals* have shown the feasibility of both prophylactic and therapeutic vaccination against *Helicobacter pylori* infection, but there have been few studies in humans. Encouraging results have been obtained with parenteral, multicomponent, aluminium hydroxide-based vaccines in terms of safety and immunogenicity. In contrast, preliminary results obtained with mucosally delivered single-component vaccines have been disappointing, partly due to the intrinsic difficulty in developing purified proteins that are sufficiently immunogenic following mucosal delivery. Studies are ongoing into the mechanisms by which the host's genetic make-up modifies the inflammatory and immunological response to *H. pylori* and the development of suitable adjuvants.[1-6]

1. Ruggiero P, *et al.* The quest for a vaccine against Helicobacter pylori: how to move from mouse to man? *Microbes Infect* 2003; 5: 749–56.
2. Sutton P, Doidge C. Helicobacter pylori vaccines spiral into the new millennium. *Dig Liver Dis* 2003; 35: 675–87.
3. Del Giudice G, Michetti P. Inflammation, immunity and vaccines for Helicobacter pylori. *Helicobacter* 2004; 9 (suppl 1): 23–8.
4. Agarwal K, Agarwal S. Helicobacter pylori vaccine: from past to future. *Mayo Clin Proc* 2008; 83: 169–75.
5. Sijun H, Yong X. *Helicobacter pylori* vaccine: mucosal adjuvant & delivery systems. *Indian J Med Res* 2009; 130: 115–24.
6. Velin D, Michetti P. Advances in vaccination against *Helicobacter pylori*. *Expert Rev Gastroenterol Hepatol* 2010; 4: 157–66.

Hepatitis A Immunoglobulins

Inmunoglobulinas contra la hepatitis A.
ATC — J06BB11.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Human Hepatitis A Immunoglobulin; Immunoglobulinum Humanum Hepatitidis A). A sterile liquid or freeze-dried preparation containing human immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having specific antibodies against the hepatitis A virus. Normal immunoglobulin may be added. It contains not less than 600 international units/mL. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container under vacuum or under an inert gas.

Profile

Immunoglobulins containing high levels of specific antibodies against hepatitis A have been used in some countries for passive immunisation against hepatitis A infection; in the UK, normal immunoglobulin is usually given.

References.

1. Liu JP, *et al.* Immunoglobulins for preventing hepatitis A. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 10/02/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Globuman Hepatite A.

Pharmacopoeial Preparations
Ph. Eur.: Human Hepatitis A Immunoglobulin.

Hepatitis A Vaccines

Vacunas de la hepatitis A.
ATC — J07BC02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Hepatitis A Vaccine (Inactivated, Adsorbed); Vaccinum Hepatitidis A Inactivatum Adsorbatum; Inactivated Hepatitis A Vaccine BP 2014). A liquid preparation of a suitable strain of hepatitis A virus grown in cell cultures, inactivated by a validated method, and adsorbed on a mineral carrier. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Hep A may be used on the label.

Ph. Eur. 8: (Hepatitis A Vaccine (Inactivated, Virosome); Vaccinum Hepatitidis A Inactivatum Virosomale). A liquid preparation of a suitable strain of hepatitis A virus grown in cell cultures and inactivated by a validated method. Virosomes composed of influenza proteins and phospholipids are used as adjuvants. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that HepA may be used on the label.

Uses and Administration

Hepatitis A vaccines are used for active immunisation against hepatitis A infection.

In the UK, the use of an inactivated vaccine is recommended as an alternative to normal immunoglobulin for frequent travellers to areas of high or moderate hepatitis A endemicity or for those staying for more than 3 months in such areas; in some countries a hepatitis A immunoglobulin (above) is available for those making shorter or less frequent journeys. Immunisation is also recommended in haemophiliacs, patients with chronic liver disease, and in those at risk of exposure to hepatitis A by virtue of their occupation, and should be considered in persons whose lifestyle is likely to place them at risk. The vaccine is given intramuscularly, except in haemophiliacs in whom it should be given by deep subcutaneous injection. In the UK, various vaccines are available and the dose (0.5 or 1 mL) depends on the product used and age of the patient. They may be prepared from several inactivated hepatitis A virus strains including CR326F, GBM, HM175, and RG-SB. The primary immunisation schedule for all vaccines consists of a single dose appropriate to the age of the patient and should be followed 6 to 12 months later by a booster dose. Immunity is provided for at least 10 years after these doses.

In the USA, immunisation from 12 to 23 months of age (with a second dose at least 6 months later) is recommended as part of the routine primary immunisation schedule. Postexposure prophylaxis is recommended in persons who have not previously received a hepatitis A vaccine. Vaccination is also recommended for travellers to countries with intermediate to high hepatitis A endemicity.

References.

1. WHO. Hepatitis A vaccines: WHO position paper. *Wkly Epidem Rec* 2000; 75: 38–44. Also available at: http://www.who.int/immunization/wer7505Hepatitis%20A_Feb00_position_paper.pdf (accessed 23/06/10)
2. American Academy of Pediatrics Committee on Infectious Diseases. Hepatitis A vaccine recommendations. *Pediatrics* 2007; 120: 189–99. http://pediatrics.aappublications.org/cgi/reprint/120/1/189.pdf (accessed 15/07/08)
3. Koslap-Petraco MB, *et al.* Hepatitis A: disease burden and current childhood vaccination strategies in the United States. *J Pediatr Health Care* 2008; 22: 3–11.
4. Nothdurft HD. Hepatitis A vaccines. *Expert Rev Vaccines* 2008; 7: 535–45.

Vaccine development. Commercially available hepatitis A vaccines are usually produced from inactivated hepatitis A virus strains propagated in cell culture, commonly of human diploid fibroblast cells. 'Virosome' hepatitis A vaccines consisting of inactivated hepatitis A virus epitopes formulated into liposomes are also becoming available. Live attenuated hepatitis A vaccines have also been developed, although an oral live vaccine does not appear to have yet been produced.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

General references.

1. Niu MT, *et al.* Two-year review of hepatitis A vaccine safety: data from the Vaccine Adverse Event Reporting System (VAERS). *Clin Infect Dis* 1998; 26: 1475–6.

Effects on the blood. WHO has received reports of 5 cases of thrombocytopenia, 3 with purpura, associated with hepatitis A vaccine.[1]

1. Meyboom RHB, *et al.* Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995; 345: 1638.

Effects on the nervous system. Neurological symptoms resembling encephalitis have followed a third dose of hepatitis A vaccine.[1] Other serious neurological reactions reported in patients given inactivated hepatitis A vaccine include transverse myelitis, Guillain-Barré syndrome, and neuralgic amyotrophy.[2] Such reactions appear to be very rare, and, since other vaccines have often been given simultaneously, may not be directly attributable to hepatitis A vaccine.

1. Hughes PJ, *et al.* Probable post-hepatitis A vaccination encephalopathy. *Lancet* 1993; 342: 302.
2. CSM/MCA Hepatitis A vaccination (Havrix). *Current Problems* 1994; 20: 16. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 23/04/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hepatitis B vaccine 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 02/11/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Avaxim; Epaxal; Havrix; VAQTA; Virohep-A; *Austral.*: Avaxim; Havrix; VAQTA; *Austria*: Avaxim; Epaxal; Havrix; *Belg.*: Epaxal; Havrix; *Braz.*: Vacina Contra Hepatite A; *Canad.*: Avaxim; Epaxal; Havrix; VAQTA; *Chile*: Avaxim; Epaxal; Havrix; *China*: Avaxim (巴维信); Epaxal (爱巴苏); Hai Wei Ke (海威克); Havrix (贺福立适); Healive (孩尔来福); VAQTA (维康特); Wei Sai Rui An (维赛瑞安); Wei Sai Rui Ji (维赛瑞吉); Cz.: Avaxim; Havrix; VAQTA; *Denm.*: Avaxim; Epaxal; Havrix; VAQTA; *Fin.*: Avaxim†; Epaxal; Havrix; VAQTA†; *Fr.*: Avaxim; Havrix; *Ger.*: Havpur; Havrix; VAQTA; *Gr.*: Avaxim; Epaxal; Havrix; VAQTA; *Hong Kong*: Avaxim; Epaxal; Havrix; VAQTA; *Hung.*: Avaxim; Havrix; VAQTA; *India*: Avaxim; Biovac-A; Havpur; Havrix; *Indon.*: Avaxim; Havrix; VAQTA; *Irl.*: Avaxim; Epaxal; Havrix; VAQTA; *Israel*: Avaxim; Epaxal; Havrix; VAQTA; *Ital.*: Avaxim; Epaxal; Havrix; VAQTA; *Malaysia*: Avaxim; Epaxal; Havrix; *Mex.*: Avaxim; Havrix; VAQTA; *Neth.*: Avaxim; Epaxal; Havrix; VAQTA; *Norw.*: Epaxal; Havrix; *NZ*: Avaxim; Epaxal†; Havrix; VAQTA; *Philipp.*: Avaxim; Epaxal; Havrix; Mevac-A; *Pol.*: Avaxim; Havrix; VAQTA; *Port.*: Avaxim; Epaxal; Havrix; VAQTA; *Rus.*: Avaxim (Аваксим); Havrix (Хаврикс); VAQTA (BAKTA); *S.Afr.*: Avaxim; Havrix; *Singapore*: Avaxim; Epaxal; Havrix; VAQTA; *Spain*: Epaxal; Havrix; VAQTA; *Swed.*: Avaxim; Epaxal; Havrix; *Switz.*: Epaxal; Havrix; *Thai.*: Avaxim; Epaxal; Havrix; VAQTA; *Turk.*: Avaxim; Epaxal; Havrix; VAQTA; *UK*: Avaxim; Epaxal; Havrix; VAQTA; *Ukr.*: Havrix (Хаврикс)†; *USA*: Havrix; VAQTA; *Venez.*: Havrix.

Pharmacopoeial Preparations

Ph. Eur.: Hepatitis A Vaccine (Inactivated, Adsorbed); Hepatitis A Vaccine (Inactivated, Virosome).

Hepatitis B Immunoglobulins

Inmunoglobulinas contra la hepatitis B.
ATC — J06BB04.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Hepatitis B Immunoglobulin; Immunoglobulinum Humanum Hepatitidis B). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected and/or immunised donors having specific antibodies against hepatitis B surface antigen. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container, under vacuum or under an inert gas.

Ph. Eur. 8: (Human Hepatitis B Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Hepatitidis B ad Usum Intravenosum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected and/or immunised donors having antibodies against hepatitis B surface antigen. Human normal immunoglobulin for intravenous administration may be added. It contains not less than 50 international units/mL. Storage requirements are similar to those for Human Hepatitis B Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25 degrees.

USP 36: (Hepatitis B Immune Globulin). A is a sterile solution consisting of globulins derived from the plasma of human donors who have high titres of antibodies against hepatitis B surface antigen. It contains 10 to 18% of protein, of which not less than 80% is monomeric immunoglobulin G. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Hepatitis B immunoglobulins are used for passive immunisation of persons exposed or possibly exposed to hepatitis B virus, including by sexual contact. They are not appropriate for treatment. Hepatitis B immunoglobulins should always be given in addition to active immunisation with hepatitis B vaccine in at-risk patients exposed to hepatitis B virus.

In the UK, a hepatitis B immunoglobulin containing 100 international units/mL is available for intramuscular use. The dose in adults and children over 10 years of age is a single dose of 500 international units by intramuscular injection given preferably within 48 hours of exposure and not more than 1 week after exposure. Children aged 5 to 9 years may be given 300 international units, and children under 5 years 200 international units. Hepatitis B immunoglobulin should also be given to newborn infants at risk whose mothers are persistent carriers of hepatitis B surface antigen or whose mothers are HBsAg-positive as a result of recent infection. The dose is 200 international units by intramuscular injection preferably at birth, and certainly within 24 hours of birth.

There is now a UK and European standard for a preparation for intravenous use containing not less than 50 international units/mL.

In the USA, a hepatitis B immunoglobulin containing 15 to 18% of protein is available for intramuscular use. The dose for adults is 0.06 mL/kg. A dose of 0.5 mL is given to infants perinatally exposed to hepatitis B; this appears to be a significantly lower dose than that used in the UK. A hepatitis B immunoglobulin is also available for the prevention of hepatitis B recurrence after liver transplantation in patients who are positive for hepatitis B surface antigen. It is given intravenously at a dose of 20 000 international units during surgery and then daily from day 1 to day 7 after transplant surgery, then every 2 weeks from week 2 to week 12, and then monthly from 4 months post-surgery.

Preparation strength. *The content of hepatitis B immunoglobulin may vary between countries and between manufacturers. Care should be taken in interpreting dosage recommendations which are not given in terms of international units.* Products available in the USA have their strength expressed with reference to an FDA standard but are considered to contain the equivalent of at least 200 international units/mL.

Monoclonal antibodies. The name tuvirumab is applied to a human hepatitis B monoclonal antibody. A murine monoclonal antibody has been tried in a few patients with primary antibody deficiency.[1]

1. Lever AML, *et al.* Monoclonal antibody to HBsAg for chronic hepatitis B virus infection with hypogammaglobulinaemia. *Lancet* 1990; 335: 1529.

Organ and tissue transplantation. Studies[1-5] in patients positive for hepatitis B surface antigen undergoing liver transplantation (p. 1936.3) suggest that long-term passive immunisation with hepatitis B immunoglobulin could reduce hepatitis B re-infection and improve survival in these patients.

1. Samuel D, *et al.* Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. *Lancet* 1991; 337: 813–15.
2. Nymann T, *et al.* Prevention of hepatitis B recurrence with indefinite hepatitis B immune globulin (HBIG) prophylaxis after liver transplantation. *Clin Transplant* 1996; 10: 663–7.
3. McGory RW, *et al.* Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation* 1996; 61: 1358–64.
4. Terrault NA, *et al.* Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. *Hepatology* 1996; 24: 1327–33.
5. Sanchez-Fueyo A, *et al.* Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: a new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology* 2000; 31: 496–501.

Postexposure prophylaxis. For discussion of the use of hepatitis B immunoglobulins in patients exposed to hepatitis B virus, see Postexposure Prophylaxis under Uses and Administration of Hepatitis B Vaccines, p. 2390.2.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Preparation strength. For a warning concerning possible lack of equivalence between different preparations of hepatitis B immunoglobulins, see under Uses and Administration, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hepatitis B immunoglobulin 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)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antib; Igantibe; *Austria*: Hepatect; Venbig; Zutectra; *Belg.*: Hepacaf; *Canad.*: HepaGam B; HyperHep B; *Chile*: Igantibe; *Cz.*: NeoHepatect; Zutectra; *Denm.*: Venbig; *Fr.*: IVheBex; Zutectra; *Ger.*: Hepatect; Zutectra; *Gr.*: Aunativ; Hepatect; Hepuman; Igantibe; Immuno HBS; IVheBex; Venbig; *Hong Kong*: Hyper Hep B; *Hung.*: Hepatect; *India*: Aunativ; Hepabig; Hepaglob; *Indon.*: HyperHep B; *Irl.*: Hepatect; Zutectra; *Israel*: HepaGam B; Hepatect; HyperHep B; Omri-Hep-B; *Ital.*: Igantibe; ImmunoHBs; Neohepatect; Uman-Big; Venbig; Zutectra; *Jpn*: Hebsbulin; *Malaysia*: Hepabig; *Neth.*: Hepatect; HepBQuin; ImmunoGam†; IVheBex; *NZ*: HyperHep B; *Philipp.*: BayHep B; Hepabig; *Pol.*: Gamma Anty HBs; Hepatect; Zutectra; *Port.*: Hepatect; IVheBex; Venbig; Zutectra; *Rus.*: Antihep (Антигеп); *S.Afr.*: Hebagam; *Spain*: Gamma Antihepatitis B†; Gammaglob Antihepatitis BP†; Hepatect; Igantibe; Niuliva; Zutectra; *Swed.*: Venbig; Zutectra; *Switz.*: Hepatect; Zutectra; *Thai.*: Igantibe; ImmunoHBs; Venbig; *Turk.*: BayHep B; Hep B Quin; Hepatect; Hepatitis B Ig-P; Hepuman; Hyper Hep B; IVheBex; *UK*: Hepatect; Zutectra; *USA*: HepaGam B; HyperHep B; Nabi-HB.

Pharmacopoeial Preparations

Ph. Eur.: Human Hepatitis B Immunoglobulin for Intravenous Administration; Human Hepatitis B Immunoglobulin;
USP 36: Hepatitis B Immune Globulin.

Hepatitis B Vaccines

Vacunas de la hepatitis B.
ATC — J07BC01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) have monographs.

Ph. Eur. 8: (Hepatitis B Vaccine (rDNA); Vaccinum Hepatitidis B (ADNr)). A preparation of hepatitis B surface antigen, that is obtained by recombinant DNA technology. It should be stored at a temperature of 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light. Under these storage conditions it may be expected to retain its potency for 24 months.

The BP 2014 states that Hep B may be used on the label.

Uses and Administration

Hepatitis B vaccines are used for active immunisation against hepatitis B infection. Two types of vaccine have been available, each containing hepatitis B surface antigen (HBsAg) adsorbed onto aluminium hydroxide or a similar adsorbent. The type of vaccine in which the surface antigen is produced in yeast cells using recombinant DNA techniques is now widely used and there has been considerable interest in further developments to improve immunogenicity. The second type of vaccine, in which the surface antigen is obtained from plasma after purification and inactivation processes is now not generally available.

WHO had recommended that national immunisation policies should include routine hepatitis B immunisation for the whole population by 1997 and this has been implemented in some countries including the USA (see Administration, p. 2390.1). The current recommendations in the UK are for immunisation of persons at high risk of contracting hepatitis B. High-risk groups include:

- healthcare personnel, laboratory workers, or any other personnel who have direct contact with patients or their body fluids or tissues
- staff and residents of accommodation for those with severe learning difficulties
- patients with chronic liver disease
- patients with chronic renal failure including those requiring haemodialysis
- haemophiliacs and those receiving regular blood transfusions or blood products
- close family contacts or sexual partners of cases or carriers of hepatitis B

- families adopting children from countries with a high prevalence of hepatitis B
- foster carers
- individuals who frequently change sexual partners
- parenteral drug abusers
- inmates of custodial institutions
- some travellers to areas where hepatitis B is endemic
- infants born to women who are persistent carriers of hepatitis B surface antigen or infants born to women who are HBsAg-positive as a result of recent infection

Hepatitis C carriers who are not immunised against hepatitis B should also receive immunisation.

A basic immunisation schedule consists of 3 doses of a hepatitis B vaccine, with the second and third doses 1 and 6 months, respectively, after the first. In the USA, some products may be given in an alternative 2-dose regimen to adolescents with doses given 4 to 6 months apart. Doses should be given intramuscularly, with the deltoid region being the preferred site in adults and older children and the anterolateral thigh the preferred site in neonates, infants, and younger children; the gluteal region (buttock) should not be used as efficacy may be reduced. The subcutaneous route should be used in patients with haemophilia. The dose of the recombinant vaccine depends on the product used. Typical doses for adults are 10 or 20 micrograms and for infants and children 5 or 10 micrograms. Products containing 40 micrograms are available for adult dialysis and predialysis patients who have a reduced immune response to the vaccine. However, *the dose of one recombinant preparation should not be seen as equivalent to the dose of another.*

For pre-exposure prophylaxis in high-risk groups and for postexposure prophylaxis an accelerated schedule should be used. It may also be used where more rapid immunisation, for instance with travellers, is required. This schedule involves giving the third dose 2 months after the initial dose with a further booster at 1 year. In exceptional circumstances in adults travelling to an endemic area who commence their vaccination course within a month of departure, an even more rapid schedule involving injections at 0, 7, and 21 days has been used; when this schedule is used, a booster dose is recommended after 1 year.

For newborn infants at risk combined active and passive immunisation against hepatitis B is recommended. The first dose of vaccine should preferably be given at birth, and certainly within 24 hours of birth. A single dose of hepatitis B immunoglobulin (200 international units) should be given at the same time into a different site. Additionally, in any patient in whom immediate protection is required, combined active and passive immunisation may be considered with a single dose of 500 international units of hepatitis B immunoglobulin being the dose for adults. See under Hepatitis B Immunoglobulins, p. 2389.2, for children's doses.

General references.

1. Buynak EB, *et al.* Vaccine against human hepatitis B. *JAMA* 1976; 235: 2832–4.
2. Douglas RG. The heritage of hepatitis B vaccine. *JAMA* 1996; 276: 1796–8.
3. Lemon SM, Thomas DL. Vaccines to prevent viral hepatitis. *N Engl J Med* 1997; 336: 196–204.
4. Keating GM, Noble S. Recombinant hepatitis B vaccine (Engerix-B): a review of its immunogenicity and protective efficacy against hepatitis B. *Drugs* 2003; 63: 1021–51.
5. WHO. Hepatitis B vaccines: WHO position paper. *Wkly Epidem Rec* 2009; 84: 405–20. Also available at: http://www.who.int/wer/2009/wer8440.pdf (accessed 22/06/10)

Administration. The major public health burden of hepatitis B infection in the developing world is due to the consequences of chronic carriage of hepatitis B virus (hepatocellular carcinoma and chronic cirrhosis) rather than acute infection. WHO[1] considered that the most important means of controlling hepatitis B on a global scale and of reducing mortality from its sequelae was mass immunisation of infants. It stated that hepatitis B vaccine should be incorporated into the Expanded Programme on Immunization (EPI) and many countries have since done so. WHO later reiterated this aim[2] stating that hepatitis B vaccine should be integrated into national immunisation programmes in all countries with a hepatitis B carrier prevalence (HBsAg) of 8% or greater by 1995 and in all countries by 1997. WHO's aim was to reduce the incidence of new child carriers of hepatitis B by 80% by 2001. Results from Taiwan, where mass immunisation of infants has been in place since the mid-1980s have shown a marked decline in the number of child carriers under 10 years of age.[3,4] The incidence of hepatocellular carcinoma in children has also been reduced.[5,6]

Opinion has been divided in the UK regarding implementation of universal hepatitis B immunisation,[7-9] with some advising increased emphasis on alternative strategies already in place such as antenatal screening.[7,8]

The optimum vaccination strategy depends on the pattern of hepatitis B viral transmission in a particular country.[10] In hyperendemic regions where most infections are acquired early in life, the vaccine should be given shortly after birth and hepatitis B immunisation integrated into the EPI. Immunisation of all infants should be considered for population groups with chronic hepatitis B virus carrier rates greater than 2% and should be a public health priority where carrier rates are greater than 10%. Countries with a lower carrier rate might opt to immunise all adolescents as an alternative to infant immunisation. Immunisation of individuals at high risk of infection should be continued in addition to routine vaccination schedules[2] and, if hepatitis B is not integrated into infant vaccination schedules, screening pregnant women for HBsAg and immunising the infants of HBsAg-positive mothers should continue.[1]

If use of hepatitis B vaccine is integrated into the EPI, 3 doses should be given intramuscularly, the first dose being given as soon as possible after birth with the first EPI immunisation. The exact timing of these doses will depend on the risk of transmission at birth and the EPI schedule in operation. In the USA, these recommendations have been implemented by immunisation of all infants and of children at any age between 2 and 18 years who have not previously received 3 doses of vaccine. The recommended schedule is for all infants to be given an initial dose of the monovalent hepatitis B vaccine soon after birth; then 2 further doses with the monovalent vaccine or 3 further doses with a combination vaccine containing hepatitis B. Infants of HBsAg-positive mothers should receive hepatitis B vaccine plus hepatitis B immunoglobulin within 12 hours of birth. Infants whose mother's HBsAg status is unknown should receive a hepatitis B vaccine within 12 hours of birth and the maternal blood should be checked at delivery and, if positive for HBsAg, the infant given hepatitis B immunoglobulin as soon as possible (no later than 1 week of age). The second dose is given at 1 to 2 months of age and the final dose at 6 months of age or later. Infants who receive a combination vaccine after the birth dose may be given an additional dose at 4 months of age. Alternatively, some products may be given in a two-dose regimen, with doses given 4 to 6 months apart.

1. WHO. Progress in the control of viral hepatitis: memorandum from a WHO meeting. *Bull WHO* 1988; 66: 443–55.
2. Anonymous. Hepatitis B vaccine. *WHO Drug Inf* 1993; 7: 130–1.
3. Chen H-L, *et al.* Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. *JAMA* 1996; 276: 906–8.
4. Hsu H-M, *et al.* Seroepidemiologic survey for hepatitis B virus infection in Taiwan: the effect of hepatitis B mass immunization. *J Infect Dis* 1999; 179: 367–70.
5. Lee C-L, Ko Y-C. Hepatitis B vaccination and hepatocellular carcinoma in Taiwan. *Pediatrics* 1997; 99: 351–3.
6. Chang M-H, *et al.* Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997; 336: 1855–9.
7. Mortimer PP, Miller E. Commentary: antenatal screening and targeting should be sufficient in some countries. *BMJ* 1997; 314: 1036–7.
8. Dunn J, *et al.* Integration of hepatitis B vaccination into national immunisation programmes: alternative strategies must be considered before universal vaccination is adopted. *BMJ* 1997; 315: 121–2.
9. Goldberg D, McMenamin J. The United Kingdom's hepatitis B immunisation strategy—where now? *Commun Dis Public Health* 1998; 1: 79–83.
10. Rots NY, *et al.* Hepatitis B vaccination strategies tailored to different endemicity levels: some considerations. *Vaccine* 2010; 28: 893–900.

BOOSTER DOSES. There has been considerable interest in the duration of immunity conferred by hepatitis B vaccination and the possible need for booster doses.[1-3]

In the UK it is now recommended that individuals at continuing risk of infection should be offered a *single* booster dose of vaccine, *once only*, about 5 years after primary immunisation. Boosters are also recommended if contamination of eyes, mouth, or fresh cuts on skin with blood from a HBsAg-positive person occurs, unless they are known to have protective concentrations of antibody. However, a meta-analysis[3] suggested that a 3-dose course of immunisation with hepatitis B vaccine in immunocompetent individuals resulted in good protection against infection for up to 20 years.

References.

1. European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000; 355: 561–5.
2. Banatvala JE, Van Damme P. Hepatitis B vaccine—do we need boosters? *J Viral Hepatitis* 2003; 10: 1–6.
3. Poorolajal J, *et al.* Long-term protection provided by hepatitis B vaccine and need for booster dose: a meta-analysis. *Vaccine* 2010; 28: 623–31.

Postexposure prophylaxis. A combination of passive immunisation with a hepatitis B immunoglobulin and active immunisation with a hepatitis B vaccine is generally recommended for postexposure prophylaxis against hepatitis B.

One group of patients who should be given postexposure prophylaxis are infants born to mothers who are persistent carriers of hepatitis B surface antigen (HBsAg). The risk is particularly high if the mother has detectable hepatitis Be antigen (HBeAg) or hepatitis B virus DNA or absence of detectable antibody to hepatitis Be antigen (anti-HBe). Postexposure prophylaxis is also recommended in the UK for persons accidentally inoculated, or who contaminate the eye or mouth or breaks to the skin with blood from a known HBsAg-positive person, as well as in sexual contacts (and sometimes close family contacts) of sufferers from acute hepatitis B and who are seen within a week of the onset of jaundice in the contact.

In the UK, the recommended schedule for postexposure prophylaxis is the first dose of vaccine given preferably within 48 hours of exposure and no later than one week after exposure, or, for neonates exposed to hepatitis B at birth, no later than 24 hours after birth, with a single dose of hepatitis B immunoglobulin given simultaneously at a separate site. The second and third doses of vaccine are given 1 and 2 months after the first dose, with a booster dose at 12 months. Healthcare workers who have been successfully immunised should be given a booster dose after subsequent contamination with blood from an infected person, unless they are known to have adequate antibody concentration.

Adverse Effects

As for vaccines in general, p. 2375.1.

In addition, abdominal pain and gastrointestinal disturbance, and musculoskeletal and joint pain and inflammation have been reported after hepatitis B vaccines. There may also be dizziness and sleep disturbance. Cardiovascular effects include occasional hypotension and, rarely, tachycardia. Other rare adverse effects include dysuria, visual disturbances, and earache.

General references.

1. McMahon BJ, *et al.* Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. *Am J Med* 1992; 92: 254–6.
2. Anonymous. Adverse events after hepatitis B vaccination. *Can Med Assoc J* 1992; 147: 1023–6.
3. Duclos P. Safety of immunisation and adverse events following vaccination against hepatitis B. *Expert Opin Drug Safety* 2003; 2: 225–31.
4. Autret-Leca E, *et al.* Tolérance du vaccin contre l'hépatite B: exemple d'une complémentarité notification spontanée/études pharmacoépidémiologiques. *Presse Med* 2007; 36: 563–4.

Effects on the blood. Rare cases of thrombocytopenia[1-4] and pancytopenia[5] associated with hepatitis B vaccination have been reported.

1. Poullin P, Gabriel B. Thrombocytopenic purpura after recombinant hepatitis B vaccine. *Lancet* 1994; 344: 1293.
2. Meyboom RHB, *et al.* Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995; 345: 1638.
3. Ronchi F, *et al.* Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine. *Arch Dis Child* 1998; 78: 273–4.
4. Nuevo R, *et al.* Thrombocytopenic purpura after hepatitis B vaccine: case report and review of the literature. *Pediatr Infect Dis J* 2004; 23: 183–4.
5. Viallard JF, *et al.* Severe pancytopenia triggered by recombinant hepatitis B vaccine. *Br J Haematol* 2000; 110: 230–3.

Effects on bones and joints. Reactive arthritis[1-3] and Reiter's syndrome[2] have been reported after hepatitis B vaccination. There have also been isolated reports of rheumatoid arthritis occurring after hepatitis B vaccination[3,4] and a suggestion that hepatitis B vaccination may trigger the onset of underlying SLE.[5] Some reports of arthralgia have been received by the UK CSM and by the manufacturers of *Engerix B*.[2]

1. Rogerson SJ, Nye PJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; 301: 345.
2. Hassan W, Oldham R. Reiter's syndrome and reactive arthritis in health care workers after vaccination. *BMJ* 1994; 309: 94–5.
3. Gross K, *et al.* Arthritis after hepatitis B vaccination: report of three cases. *Scand J Rheumatol* 1995; 24: 50–2.
4. Pope JE, *et al.* The development of rheumatoid arthritis after recombinant hepatitis B vaccination. *J Rheumatol* 1998; 25: 1687–93.
5. Maillefert JF, *et al.* Rheumatic disorders developed after hepatitis B vaccination. *Rheumatology (Oxford)* 1999; 38: 978–83.

Effects on the eyes. There have been isolated case reports of acute posterior uveitis,[1] visual loss associated with eosinophilia,[2] acute posterior multifocal placoid pigment epitheliopathy,[3] central retinal vein occlusion,[4] and multiple evanescent white dot syndrome[5] after vaccination against hepatitis B.

For mention of optic neuritis in patients receiving hepatitis B vaccine, see under Effects on the Nervous System, p. 2391.1.

1. Fried M, *et al.* Uveitis after hepatitis B vaccination. *Lancet* 1987; ii: 631–2.
2. Brézin AP, *et al.* Visual loss and eosinophilia after recombinant hepatitis B vaccine. *Lancet* 1993; 342: 563–4.
3. Brézin AP, *et al.* Acute posterior multifocal placoid pigment epitheliopathy after hepatitis B vaccine. *Arch Ophthalmol* 1995; 113: 297–300.
4. Devin F, *et al.* Occlusion of central retinal vein after hepatitis B vaccination. *Lancet* 1996; 347: 1626.
5. Baglivo E, *et al.* Multiple evanescent white dot syndrome after hepatitis B vaccine. *Am J Ophthalmol* 1996; 122: 431–2.

Effects on the kidneys. There have been case reports of acute glomerulonephritis in patients after hepatitis B vaccine.[1,2]

1. Carmeli Y, Oren R. Hepatitis B vaccine side-effect. *Lancet* 1993; 341: 250–1.
2. Pennesi M, *et al.* Glomerulonephritis after recombinant hepatitis B vaccine. *Pediatr Infect Dis J* 2002; 21: 172–3.

Effects on the liver. There have been occasional reports of transient abnormalities in liver function associated with hepatitis B vaccine.[1-3] The appearance of autoantibodies

has been reported in a patient,[2] and severe cytolysis consistent with an allergic mechanism in another.[3]

1. Rajendran V, Brooks AP. Symptomatic reaction to hepatitis B vaccine with abnormal liver function values. *BMJ* 1985; 290: 1476.
2. Lilic D, Ghosh SK. Liver dysfunction and DNA antibodies after hepatitis B vaccination. *Lancet* 1994; 344: 1292–3.
3. Germanaud J, *et al.* A case of severe cytolysis after hepatitis B vaccination. *Am J Med* 1995; 98: 595.

Effects on the nervous system. In the years 1982 to 1985 the Centers for Disease Control, the FDA, and the manufacturer of plasma-derived hepatitis B vaccine received 41 reports of adverse neurological effects.[1] It was estimated that about 850 000 persons had received the vaccine in this time. Neurological events were convulsions (5 cases), Bell's palsy (10 cases), Guillain-Barré syndrome (9 cases), lumbar radiculopathy (5 cases), brachial plexus neuropathy (3 cases), optic neuritis (5 cases), and transverse myelitis (4 cases). In some analyses Guillain-Barré syndrome was reported significantly more often than expected. However, no conclusive epidemiological association could be made between any neurological adverse effect and the vaccine.

In France, spontaneous reports of multiple sclerosis and central demyelinating disease in patients who had received hepatitis B vaccine led to the suspension by the French authorities of hepatitis B vaccination in schools in 1998. This decision was widely condemned by many authorities including WHO, the US National Multiple Sclerosis Society, and the Viral Hepatitis Prevention Board, and there was a fear that reduced confidence in the vaccine could have a profound effect on uptake. Arguments[2] against a link between hepatitis B vaccine and multiple sclerosis include the lack of correlation between the incidence of hepatitis B infection and demyelinating diseases, data from clinical studies including extensive postmarketing surveillance, and analysis of the French cases which concluded that the incidence of multiple sclerosis amongst vaccine recipients was not higher than would be expected in the population as a whole. A consultative group concluded[3] that, in the light of the evidence, the benefits of hepatitis B vaccination supported current WHO recommendations that all countries should have universal infant and/or adolescent hepatitis B immunisation programmes and that adults at increased risk of infection should also be immunised. More recent studies[4,5] have also indicated no association between hepatitis B vaccine and multiple sclerosis, although one study[6] did suggest a threefold increase in risk.

A case-control analysis[7] reported that vaccination with a hepatitis B vaccine did not generally increase the risk of CNS inflammatory demyelination in childhood. However, data from vaccination with one specific hepatitis B vaccine (*Engerix B*) suggested a small risk increase, particularly for confirmed multiple sclerosis, in the longer term. A review[8] noted that in addition to reports of neuropathies there had also been reports of a temporal association of hepatitis B vaccination with myasthenia gravis, polyarteritis nodosa, and dermatomyositis, but that evidence was largely confined to weak case reports and could not be used to confirm causality.

1. Shaw FE, *et al.* Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination: experience of the first three years. *Am J Epidemiol* 1988; 127: 337–52.
2. Anonymous. Expanded Programme on Immunization (EPI): lack of evidence that hepatitis B vaccine causes multiple sclerosis. *Wkly Epidem Rec* 1997; 72: 149–52.
3. Halsey NA, *et al.* Hepatitis B vaccine and central nervous system demyelinating diseases. *Pediatr Infect Dis J* 1999; 18: 23–4.
4. Ascherio A, *et al.* Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001; 344: 327–32.
5. Mikaeloff Y, *et al.* Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. *Arch Pediatr Adolesc Med* 2007; 161: 1176–82.
6. Hernán MA, *et al.* Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. *Neurology* 2004; 63: 838–42.
7. Mikaeloff Y, *et al.* Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. *Neurology* 2009; 72: 873–80.
8. Stübgen J-P. Neuromuscular disorders associated with hepatitis B vaccination. *J Neurol Sci* 2010; 292: 1–4.

Effects on the skin. Skin reactions, which have been reported in a few individuals after hepatitis B vaccination, include erythema multiforme,[1,2] erythema nodosum,[3-5] lichen planus,[6-8] and vasculitis.[9]

1. Peldshon SD, Sampliner RE. Reaction to hepatitis B virus vaccine. *Ann Intern Med* 1984; 100: 156–7.
2. Wakeel RA, White MI. Erythema multiforme associated with hepatitis B vaccine. *Br J Dermatol* 1992; 126: 94–5.
3. Di Giusto CA, Bernhard JD. Erythema nodosum provoked by hepatitis B vaccine. *Lancet* 1986; ii: 1042.
4. Goolsby PL. Erythema nodosum after Recombivax HB hepatitis B vaccine. *N Engl J Med* 1989; 321: 1198–9.
5. Rogerson SJ, Nye FJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; 301: 345.
6. Ciaccio M, Rebora A. Lichen planus following HBV vaccination: a coincidence? *Br J Dermatol* 1990; 122: 424.
7. Fernnado MF, *et al.* Lichen planus following hepatitis B vaccination. *Br J Dermatol* 1998; 139: 350.
8. Usman A, *et al.* Lichenoid eruption following hepatitis B vaccination: first North American case report. *Pediatr Dermatol* 2001; 18: 123–6.
9. de Carvalho JF, *et al.* Systemic polyarteritis nodosa following hepatitis B vaccination. *Eur J Intern Med* 2008; 19: 575–8.

Hypersensitivity. There have been reports of hypersensitivity reactions after hepatitis B vaccination that have been attributed to components of the vaccines, including formaldehyde,[1] thiomersal,[2] and *Saccharomyces cerevisiae*.[3]

1. Ring J. Exacerbation of eczema by formalin-containing hepatitis B vaccine in formaldehyde-allergic patient. *Lancet* 1986; ii: 522–3.
2. Noel L *et al.* Hypersensitivity to thiomersal in hepatitis B vaccine. *Lancet* 1991; 338: 705.
3. Brightman CAJ, *et al.* Yeast-derived hepatitis B vaccine and yeast sensitivity. *Lancet* 1989; i: 903.

Precautions

As for vaccines in general, p. 2375.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hepatitis B vaccine 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 02/11/11)

Reduced immune response. The immune response to hepatitis B vaccine is dependent on both host- and immunisation-related factors.[1] Host-related factors that appear to diminish the response include increasing age, increasing body-weight, smoking,[1,2] and male sex;[3] particular HLA haplotypes may also be associated with poor response.[4] Failure of hepatitis B immunisation in infants could be related to high perinatal maternal viraemia[5] rather than to inherent resistance to the vaccine.

Some studies have found a defective response in chronic alcoholics[6,7] whereas others have not;[8] the degree of liver impairment may be a significant factor. It has been suggested that an increased dose of hepatitis B vaccine may be appropriate in those with a history of alcoholism.[9] Active infection with *Schistosoma mansoni* also appears to decrease the response to hepatitis B vaccination.[10] A diminished response occurs in HIV-positive patients[11-13] and in patients on haemodialysis;[1] an increased dose of hepatitis B vaccine is recommended in these patients. In patients with haemophilia who are not HIV-positive[14] immunity is reported to wane rapidly after vaccination and frequent booster doses may be required. Biological response modifiers such as thymopentin[15] and interferon[16] have been used successfully in some patients on haemodialysis to overcome the immune deficit. Use of interleukin-2 has met with variable success. Granulocyte-macrophage colony-stimulating factor has also been investigated as an adjuvant for hepatitis B vaccination in healthy subjects, patients with chronic renal failure or on haemodialysis, and in HIV-infected patients. Overall, the colony-stimulating factor appears to improve seroconversion rates and antibody titres, but further study is needed.[17]

The immune response to hepatitis B vaccine is affected by the site of intramuscular injection. The deltoid region is recommended for adults and the anterolateral thigh for infants. A diminished response has been associated with injection into the gluteal region (buttock).[1]

A related problem is posed by subjects who become infected with hepatitis B despite mounting an adequate response to immunisation. In one study, evidence of viral replication was detected in 44 of 1590 hepatitis B vaccinees despite development of protective titres of antibody.[18] Acute hepatitis occurred in one patient. Although the infection may have been incubating at the time of vaccination, the virus isolated from the child with acute disease was an escape mutant with a different DNA sequence from that isolated from the mother.

1. Hollinger FB. Factors influencing the immune response to hepatitis b vaccine, booster dose guidelines, and vaccine protocol recommendations. *Am J Med* 1989; 87 (suppl 3A): 36S–40S.
2. Horowitz MM, *et al.* Duration of immunity after hepatitis B vaccination: efficacy of low-dose booster vaccine. *Ann Intern Med* 1988; 108: 185–9.
3. Morris CA, *et al.* Intradermal hepatitis B immunization with yeast-derived vaccine: serological response by sex and age. *Epidemiol Infect* 1989; 103: 387–94.
4. Alper CA, *et al.* Genetic prediction of nonresponse to hepatitis B vaccine. *N Engl J Med* 1989; 321: 708–12.
5. del Canho R, *et al.* Failure of neonatal hepatitis B vaccination: the role of HBV-DNA levels in hepatitis B carrier mothers and HLA antigens in neonates. *J Hepatol* 1994; 20: 483–6.
6. Degos F, *et al.* Hepatitis B vaccination and alcoholic cirrhosis. *Lancet* 1983; ii: 1498.
7. Mendenhall C, *et al.* Hepatitis B vaccination: response of alcoholic with and without liver injury. *Dig Dis Sci* 1988; 33: 263–9.
8. McMahon BJ, *et al.* Response to hepatitis B vaccine in Alaska Natives with chronic alcoholism compared with non-alcoholic control subjects. *Am J Med* 1990; 88: 460–4.
9. Rosman AS, *et al.* Efficacy of a high and accelerated dose of hepatitis B vaccine in alcoholic patients: a randomized clinical trial. *Am J Med* 1997; 103: 217–22.
10. Ghaffar YA, *et al.* Response to hepatitis B vaccine in infants born to mothers with schistosomiasis. *Lancet* 1989; ii: 272.
11. Carne CA, *et al.* Impaired responsiveness of homosexual men with HIV antibodies to plasma derived hepatitis B vaccine. *BMJ* 1987; 294: 866–8.
12. Collier AC, *et al.* Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. *Ann Intern Med* 1988; 109: 101–5.
13. Chan W, *et al.* Response to hepatitis B immunization in children with hemophilia: relationship to infection with human immunodeficiency virus type 1. *J Pediatr* 1990; 117: 427–30.
14. Maris JM, *et al.* Loss of detectable antibody to hepatitis B surface antigen in immunized patients with hemophilia but without human immunodeficiency virus infection. *J Pediatr* 1995; 126: 269–71.
15. Donati D, Gastaldi L. Controlled trial of thymopentin in hemodialysis patients who fail to respond to hepatitis B vaccination. *Nephron* 1988; 50: 133–6.
16. Quiroga JA, Carreño V. Interferon and hepatitis B vaccine in haemodialysis patients. *Lancet* 1989; i: 1264.
17. Cruciani M, *et al.* Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis. *Vaccine* 2007; 25: 709–18.
18. Carman WF, *et al.* Vaccine-induced escape mutant of hepatitis B virus. *Lancet* 1990; 336: 325–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: AGB; Biovac HB; Engerix-B; HBVaxPro; Hepativax; Supervax; *Austral.*: Engerix-B; H-B-Vax II; *Austria*: Engerix-B; HBVaxPro; *Belg.*: Engerix-B; Fendrix; HBVaxPro; *Braz.*: Vacina Contra Hepatite B; *Canad.*: Engerix-B; Recombivax HB; *Chile*: Engerix-B; Heberbiovac HB; Hepavax-Gene; Recomvax B; *China*: Engerix-B (安在时); Hepavax-Gene (益可欣); *Cz.*: Engerix-B; Fendrix; HBVaxPro; *Denm.*: Engerix-B; Fendrix†; HBVaxPro; *Fin.*: Engerix-B; *Fr.*: Engerix-B; Fendrix†; GenHevac B; HBVaxPro; *Ger.*: Engerix-B; Fendrix; HBVaxPro; *Gr.*: Engerix-B; Fendrix; HBVaxPro; Recombivax; *Hong Kong*: Engerix-B; H-B-Vax II†; HBVaxPro; Hepavax-Gene; Sci-B-Vac; *Hung.*: Engerix-B; HBVaxPro; *India*: Bevac; Biovac-B; Engerix-B; Enivac-HB; Genevac-B; HB Vac; Hepaccine-B; Hepagen-Plus; Hepashield; Invac-B; LG Euvax B; Shanvac-B; *Indon.*: Engerix-B; Euvax B; H-B-Vax II; Hepavax†; *Irl.*: Engerix-B; Fendrix; HBVaxPro; *Israel*: Engerix-B; Recombinant H-B Vax II; Sci-B-Vac; *Ital.*: Engerix-B; Fendrix; HBVaxPro; *Malaysia*: Engerix-B; Euvax B; HBVaxPro; Hepavax-Gene; *Mex.*: Engerix-B; H-B-Vax II; Heberbiovac HB; Probivac-B; *Neth.*: Engerix-B; Fendrix; HB-Vax-DNA†; HBVaxPro; *Norw.*: Engerix-B; Fendrix; *NZ*: Engerix-B; H-B-Vax II†; HBVaxPro; *Philipp.*: Amvax; Engerix-B; Euvax B; Genvac-B; Hepavax-Gene; Hepliv; Recomvax B†; Shanvac-B; Temrevac-HB; *Pol.*: Engerix-B; Euvax B; HBVaxPro; Hepavax-Gene; *Port.*: Engerix-B; Fendrix; HBVaxPro; *Rus.*: Biovac-B (Биовак-в)†; Engerix-B (Энджерикс В); H-B-Vax II (H-B-Вакс II); Regevac B (Регевак В); Shanvac-B (Шанвак-В); *S.Afr.*: Engerix-B; H-B-Vax II†; Heberbiovac HB; Hepaccine-B†; *Singapore*: Engerix-B; HBVaxPro; *Spain*: Engerix-B; Fendrix; HBVaxPro; *Swed.*: Engerix-B; Fendrix; HBVaxPro; *Switz.*: Engerix-B; HBVaxPro; *Thai.*: Engerix-B; Euvax B; H-B-Vax II†; HBVaxPro; Heberbiovac HB; Hepavax-Gene; Revac-Bmcf; Shanvac-B; *Turk.*: Engerix-B; Euvax B; GenHevac B; HBVaxPro; Hepavax-Gene; *UK*: Engerix-B; Fendrix; HBVaxPro; *Ukr.*: Engerix-B (Энджерикс-В); *USA*: Engerix-B; Recombivax HB; *Venez.*: Engerix-B.

Pharmacopoeial Preparations

Ph. Eur.: Hepatitis B Vaccine (rDNA).

Hepatitis A and B Vaccines

Vacunas de las hepatitis A y B.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Hepatitidis A Inactivatum et Hepatitidis B (ADNr) Adsorbatum; Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine BP 2014). A suspension consisting of a suitable strain of hepatitis A virus, grown in cell cultures and inactivated by a validated method, and of hepatitis B surface antigen obtained by recombinant DNA technology; the antigens are adsorbed on a mineral carrier, such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that HepA/HepB may be used on the label.

Uses and Administration

Combined hepatitis A and B vaccines are used for active immunisation against hepatitis A and hepatitis B.

A hepatitis A and B vaccine (*Twinrix, GSK*) is available containing not less than 720 ELISA units of inactivated hepatitis A virus and not less than 20 micrograms of recombinant hepatitis B surface antigen (HBsAg) protein in 1 mL. For primary immunisation, three doses of 1 mL are given by intramuscular injection, with the second and third doses 1 and 6 months after the first. For children up to the age of 16 years a 0.5-mL dose is given.

Alternatively, in exceptional circumstances when travel is anticipated within one month or more after the first dose but when insufficient time is available for the standard course, adults may be given an accelerated schedule. In the UK, this consists of three doses at 0, 7 and 21 days. In the US the recommended schedule consists of doses at 0, 7, and 21 to 30 days plus a dose at 12 months.

Booster doses may be given as appropriate with the monovalent component vaccines since protection against hepatitis A and B declines at different rates, or a booster dose of the combined vaccine may be given after 5 years in adults

or 4 years in children. A booster is recommended 1 year after the accelerated schedule.

In the UK a similar vaccine (*Ambirix, GSK*) is licensed for primary immunisation in a 2-dose schedule for children aged 1 to 15 years; the second dose is given between 6 and 12 months after the first.

Reviews.

1. Murdoch DL, *et al.* Combined hepatitis A and B vaccines: a review of their immunogenicity and tolerability. *Drugs* 2003; 63: 2625–49.
2. Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. *Expert Rev Vaccines* 2004; 3: 249–67.
3. Zuckerman JN. Vaccination against hepatitis A and B: developments, deployment and delusions. *Curr Opin Infect Dis* 2006; 19: 456–9.
4. Hewlett AT. Combined hepatitis A and B vaccine: providing a bright future for preventing hepatitis. *Expert Opin Biol Ther* 2009; 9: 1235–40.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Hepatitis A Vaccines, p. 2389.1, and Hepatitis B Vaccines, p. 2390.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined hepatitis A and B vaccine 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 02/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Twinrix; *Austral.*: Twinrix; *Austria*: Twinrix; *Belg.*: Twinrix; *Braz.*: Vacina Comb. Contra Hepatite A e B; *Canad.*: Twinrix; *Chile*: Twinrix; *China*: Bilive (倍尔来); Twinrix (双福立适); *Cz.*: Ambirix; Twinrix; *Denm.*: Ambirix; Twinrix; *Fin.*: Twinrix; *Fr.*: Twinrix; *Ger.*: Twinrix; *Gr.*: Twinrix; *Hong Kong*: Twinrix; *Hung.*: Twinrix; *Indon.*: Twinrix; *Irl.*: Ambirix; Twinrix; *Israel*: Twinrix; *Ital.*: Twinrix; *Malaysia*: Twinrix; *Mex.*: Twinrix; *Neth.*: Ambirix; Twinrix; *Norw.*: Twinrix; *NZ*: Twinrix; *Philipp.*: Twinrix; *Pol.*: Ambirix; Twinrix; *Port.*: Ambirix; Twinrix; *S.Afr.*: Twinrix; *Singapore*: Twinrix; *Spain*: Twinrix; *Swed.*: Ambirix; Twinrix; *Switz.*: Twinrix; *Thai.*: Twinrix; *Turk.*: Twinrix; *UK*: Ambirix; Ambrix; Twinrix; *Ukr.*: Twinrix (Твинрикс); *USA*: Twinrix; *Venez.*: Twinrix.

Pharmacopoeial Preparations

Ph. Eur.: Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine (Adsorbed).

Hepatitis A and Typhoid Vaccines

Vacunas de la hepatitis A y fiebre tifoidea.

ATC — J07CA10.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Hepatitis A (Inactivated, Adsorbed) and Typhoid Polysaccharide Vaccine; Vaccinum Hepatitidis A Inactivatum Adsorbatum et Febris Typhoidis Polysaccharidicum). A suspension consisting of a suitable strain of hepatitis A virus, grown in cell cultures and inactivated by a validated method, and of purified Vi capsular polysaccharide obtained from *Salmonella typhi* Ty 2 strain or some other suitable strain that has the capacity to produce Vi polysaccharide. The product is presented either as a liquid mixture containing both components or as 2 separate liquids which are mixed together immediately before use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

Combined hepatitis A and typhoid vaccines are used for active immunisation. They contain either inactivated HM175 or GBM hepatitis A virus strains together with the Vi capsular polysaccharide from *Salmonella typhi* Ty 2 strain. Adults and adolescents over 15 years of age may be given a dose of 1 mL by intramuscular injection, at least 2 weeks before the risk of exposure to typhoid and hepatitis A. A booster dose may be given after 6 to 12 months to provide long-term protection.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Vivaxim; *Austria*: Hepatyrix; VIATIM; *Canad.*: Vivaxim; *Fr.*: Tyavax; *Ger.*: Hepatyrix; VIATIM; *Hong Kong*: Vivaxim; *Irl.*: Hepatyrix; VIATIM; *Israel*: Hepatyrix; *Malaysia*: Vivaxim; *Neth.*: VIATIM; *NZ*: Hepatyrix; Vivaxim; *Port.*: VIATIM; *UK*: Hepatyrix; VIATIM.

Herpes Simplex Vaccines

Vacunas del herpes común; Vacunas del herpes simple.

Profile

Several types of vaccines against herpes simplex virus types 1 and 2 have been developed. They have been tried both in oral and genital herpes infections. They are also being studied for the prevention of infection in sexual partners of patients with genital herpes.

Herpes simplex virus types 1 and 2 are widespread in populations throughout the world. Herpes simplex virus type 2 causes lifelong infection with significant morbidity. Even with the availability of effective antiviral therapy, the increasing burden of herpes simplex virus infection makes it a suitable candidate for vaccine development. The incidence of neonatal herpes infections has also increased and this risk would also be addressed by development of appropriate vaccines. An additional benefit would be a reduced risk of acquiring HIV infection.

Vaccines for herpes simplex were first studied in the 1920s and many different types of vaccine have undergone evaluation. They have included auto-inoculation of live herpes simplex virus, whole inactivated vaccines, attenuated live virus vaccines, modified live virus subunit vaccines, cell culture-derived subunit vaccines, recombinant glycoprotein subunit vaccines, disabled infectious single cycle (DISC) vaccines, and nucleic acid (DNA) vaccines.[1,2]

Prophylactic vaccines against HSV-2 could be beneficial if they either shift the threshold of infection i.e. increase the titre of virus necessary to cause infection, or if they prevent clinical disease itself. An attenuated live virus vaccine based on modified HSV-1 has been tested in clinical studies but was poorly tolerated at the doses required to elicit an immune response. Prophylactic vaccines including subunit vaccines encoding virus glycoproteins and delivered with adjuvants have shown some benefits.[1,2]

To date, no randomised clinical studies have shown useful benefit from therapeutic vaccines for HSV-1 or HSV-2. A therapeutic vaccine should prevent recurrences or at least minimise their severity or duration. Heat killed, whole virus vaccines from HSV-1 (Lupidon H) and HSV-2 (Lupidon G), and inactivated subunit vaccines have been studied but have generally produced disappointing results.[1,2] Recombinant glycoprotein vaccines have also been tested but again results have been disappointing.[1,2]

1. Morrison LA. Vaccines against genital herpes: progress and limitations. *Drugs* 2002; 62: 1119–29.
2. Stanberry LR. Clinical trials of prophylactic and therapeutic herpes simplex virus vaccines. *Herpes* 2004; 11 (suppl 3): 161A–169A.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Lupidon G; Lupidon H; *Rus.*: Herpovax (Герповакс); Vitaherpavac (Витагерпавак); *Switz.*: Lupidon H+G.

Human Papillomavirus Vaccines

HPV Vaccines; Human Papilloma Virus Vaccines; Vacunas del virus del papiloma humano.

ATC — J07BM01.

UNII — 23CVL7WF4J (human papillomavirus antigen); 61746O90DY (human papillomavirus type 6 L1 capsid protein antigen); Z845VHQ61P (human papillomavirus type 11 L1 capsid protein antigen); 6LTE2DNX63 (human papillomavirus type 16 L1 capsid protein antigen); J2D279PEMS (human papillomavirus type 18 L1 capsid protein antigen); 7XB76X2V7T (human papillomavirus type 16 L1 capsid protein residues 2-471 antigen); M7H9CF9G0Z (human papillomavirus type 18 L1 capsid protein residues 2-472 antigen).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Human Papillomavirus Vaccine (rDNA); Vaccinum Papillomaviri Humani (ADNr)). A preparation of purified virus-like particles composed of the major capsid protein of one or more human papillomavirus (HPV) genotypes, that is obtained by recombinant DNA technology. It may contain an adjuvant. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

A quadrivalent recombinant human papillomavirus (HPV) vaccine, prepared from purified virus-like particles of the capsid protein L1, is used in girls and women from 9 to 26 years of age to prevent diseases such as genital warts, cervical cancer, and other pre-cancerous lesions (cervical, vulvar, and vaginal) caused by HPV types 6, 11, 16, and 18. In the USA it is also licensed for the prevention of vulvar and vaginal cancers, as well as for boys and men from 9 to 26 years of age to prevent genital warts, and in both groups for the prevention of anal cancer and anal intraepithelial neoplasia. It is also being studied for the prevention of cervical cancer in women between 27 and 45 years of age.

It is given in 3 doses of 0.5 mL intramuscularly. The first dose may be given at any time between 9 and 26 years of age; the second dose is given 2 months later, and the third dose 6 months after the first dose.

A similar bivalent recombinant HPV vaccine, prepared from a mixture of L1 capsid proteins of HPV types 16 and 18 and containing an adjuvant AS04, is licensed for the prevention of cervical cancer and pre-cancerous cervical lesions in girls and women from 9 to 25 years of age (or between 10 and 45 years of age in Australia). In Europe it is also licensed for the prevention of pre-cancerous vulvar and vaginal lesions. It is given intramuscularly in 3 doses of 0.5 mL. The first dose may be given at any age in the approved range; the second dose is given 1 month later, and the third dose 6 months after the first dose.

Further vaccines are under investigation for the treatment or prophylaxis of genital warts and several malignant neoplasms.

Reviews and studies.

1. Keam SJ, Harper DM. Human papillomavirus types 16 and 18 vaccine (recombinant, AS04 adjuvanted, adsorbed) (Cervarix®). *Drugs* 2008; 68: 359–72.
2. Stanley M. HPV vaccines: are they the answer? *Br Med Bull* 2008; 88: 59–74.
3. Huang CM. Human papillomavirus and vaccination. *Mayo Clin Proc* 2008; 83: 701–6.
4. Flaherty DK. Alkhateeb FM. Human papillomavirus quadrivalent vaccine: a look behind the numbers. *Ann Pharmacother* 2009; 43: 740–4.
5. Muñoz N, *et al.* Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. *Lancet* 2009; 373: 1949–57.
6. Romanowski B, *et al.* GlaxoSmithKline Vaccine HPV-007 Study Group. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. *Lancet* 2009; 374: 1975–85.
7. Kenter GG, *et al.* Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. *N Engl J Med* 2009; 361: 1838–47.
8. WHO. Human papillomavirus vaccines: WHO position paper. *Wkly Epidem Rec* 2009; 84: 118–31. Also available at: http://www.who.int/wer/2009/wer8415.pdf (accessed 23/06/10)
9. Campo MS, Roden RB. Papillomavirus prophylactic vaccines: established successes, new approaches. *J Virol* 2010; 84: 1214–20.
10. Garland SM, Smith JS. Human papillomavirus vaccines: current status and future prospects. *Drugs* 2010; 70: 1079–98.
11. McCormack PL, Joura EA. Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (Gardasil): a review of its use in the prevention of premalignant genital lesions, genital cancer and genital warts in women. *Drugs* 2010; 70: 2449–74.
12. Palefsky JM, *et al.* HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011; 365: 1576–85.
13. Garnock-Jones KP, Giuliano AR. Quadrivalent human papillomavirus (HPV) types 6, 11, 16, 18 vaccine: for the prevention of genital warts in males. *Drugs* 2011; 71: 591–602.
14. Giuliano AR, *et al.* Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *N Engl J Med* 2011; 364: 401–11. Correction. *ibid.*: 1481.
15. McKeage K. Romanowski B. AS04-adjuvanted human papillomavirus (HPV) types 16 and 18 vaccine (Cervarix): a review of its use in the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic HPV types. *Drugs* 2011; 71: 465–88.
16. Swedish KA, *et al.* Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. *Clin Infect Dis* 2012; 54: 891–8.

Vaccine development and efficacy. There are more than 100 known human papillomavirus (HPV) genotypes; at least 13 of these can cause cervical cancer and are also associated with other anogenital cancers and cancers of the head and neck. Genotypes 16 and 18 cause about 70% of all cervical cancers, while genotypes 6 and 11 can cause genital warts. HPV is highly transmissible with risk of infection being highest soon after sexual activity begins. Asymptomatic and transient infection occurs in most people at some time in their life. However, the fact that more than 99% of cases of cervical cancer diagnosed are associated with the presence of sexually transmitted human papillomavirus DNA has prompted the possibility of vaccine development.

Viral recombinant proteins are being studied as antigenic components of both prophylactic and therapeutic vaccines.[1-9] Prophylactic vaccines are based on the recombinant capsid proteins L1 or L2 which self-assemble into virus-like particles which induce antibodies that in turn neutralise the infecting virus. Two such vaccines (a quadrivalent HPV vaccine effective against types 6, 11, 16, and 18 and a bivalent, adjuvanted HPV vaccine effective against types 16 and 18) are licensed in several countries. The bivalent vaccine was also reported to be effective against non-vaccine types 31, 33, and 45.[10] The prophylactic vaccines have no therapeutic effects and therefore cannot be given to women with persistent HPV infection, who are at risk of developing cervical cancer. Furthermore, vaccination does not appear to provide protection against progression to cervical intraepithelial neoplasia induced by HPV present at the time of vaccination. However, analysis of pooled data from 2 follow-up studies[11] found that, irrespective of causal HPV type, previous vaccination with